89-368

Supreme Court, U.S.
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No. 89-

IN THE
Supreme Court of the United States
OCTOBER TERM, 1989

MERCK & CO., INC.,
Petitioner,

v.

BIOCRAFT LABORATORIES, INC.,
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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QUESTIONS PRESENTED

This petition presents the following questions:

1. In the guise of reviewing the question of obviousness as a matter of law under Section 103 of the Patent Act, has not the Federal Circuit usurped the Trial Court's function as the finder of fact as to the "basic factual inquiries" as established by this Court in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), thereby vitiating Rule 52(a) of the Federal Rules of Civil Procedure and the traditional roles of trial versus appellate courts?

To resolve this question, the Court will be presented with these subsidiary questions:

> Was not the Trial Court's finding that the '813 prior art patent failed to disclose or suggest Merck's patented combination of 5 mg of amiloride and 50 mg of hydrochlorothiazide a finding of fact as to the scope and content of the prior art which should not have been disturbed without applying the "clearly erroneous" standard of Rule 52(a)?
>
> Did not the Federal Circuit majority engage in improper fact finding when it found that the '430 invention was discovered by mere routine experimentation which produced only predictable results?

2. Did not the Federal Circuit's construction of Section 103 run afoul of the spirit and language of that Statute, as well as the constitutional goal of promoting the progress of science and useful arts, when that construction rendered obvious and unpatentable a new and useful medicine, made available to the public only after years of research, which was nothing more than one of the over one thousand possible combinations of ingredients contemplated by the prior art?

STATEMENT PURSUANT TO RULE 28.1

The subsidiaries (except wholly-owned subsidiaries) and affiliates of Petitioner Merck & Co., Inc. are as follows:

Ace Limited
Alta-Berkely Eurofund Limited
AMRAD Corporation Limited
AMRAD Pharmaceuticals Pty. Limited
Arramara Teoranta
A.S.C. Services Co., Ltd.
Astra/Merck, Inc.
Banyu Pharmaceutical Co., Limited
Crop Genetics International N.V.
CW Ventures
Exel Limited
ImmuLogic Pharmaceutical Corporation
Istituto Di Ricerche Di Biologia Molecolare S.p.A.
Johnson & Johnson—Merck Consumer Pharmaceuticals
Kelp Industries Pty. Limited
Kiinteisto Oy Irmelinpesa
Kronans Drughandel AB
Laboratories Prosalud, S. de R.L. de C.V.
Maquifar S. de R.L. de C.V.
Merck Sharp & Dohme of Pakistan Limited
Merind Limited
New Enterprise Associates II, L.P.
New Enterprise Associates III, Limited Partnership
Nippon Merck-Banyu Co., Limited
Panlabs, Inc.
Prodome Farmaceutica e Exportadora Ltda.
Prodome Quinica e Farmaceutica Ltda.

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MERCK & CO., INC.,

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v.

BIOCRAFT LABORATORIES, INC.,

Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Petitioner Merck & Co., Inc. ("Merck") respectfully prays that a Writ of Certiorari issue to review the judgment of the United States Court of Appeals for the Federal Circuit in Appeal No. 88-1513. Merck submits that the majority panel of the Federal Circuit here was clearly in error in reversing the judgment of the District Court and declaring Merck's United States Letters Patent No. 3,781,430 (the "'430 patent") invalid for obviousness. The majority ignored the requirements of Rule 52(a) of the Federal Rules of Civil Procedure and contravened the precedents of this Court by disregarding key factual findings of the District Court and making *de novo* findings.

This case is worthy of review to ensure that the Federal Circuit, like the other circuit courts, performs its

appropriate and limited function as an appellate court and does not invade the exclusive province of the district courts by engaging in *de novo* fact finding. In addition, the judgment of the Federal Circuit should be reviewed because the interpretation of the question of obviousness employed by the majority here will undermine pharmaceutical patents and discourage the painstaking and costly research typically required for the discovery of new and beneficial medicines.

OPINIONS BELOW

The Federal Circuit's opinion is reported at 874 F.2d 804 and is reprinted as Appendix A ("App. A") at pages 1a-15a. The opinion of the United States District Court for the District of New Jersey (Politan, J.) is reported at 690 F. Supp. 1376 and is reprinted as Appendix B ("App. B") at pages 16a-35a.

JURISDICTION

Merck seeks review by this Court of the Federal Circuit's May 10, 1989 judgment. The Federal Circuit subsequently denied Merck's Petition for Rehearing on June 7, 1989 and declined Merck's Suggestion for Rehearing In Banc on July 3, 1989. This Court has jurisdiction by virtue of 28 U.S.C. § 1254(1), and this Petition is timely by virtue of 28 U.S.C. § 2101(c) and Supreme Court Rules 20.2 and 20.4.

CONSTITUTIONAL PROVISIONS, STATUTES AND RULES INVOLVED

United States Constitution, Article I, Section 8, Clause 8:

> "Congress shall have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

35 U.S.C. Section 103:

> "Conditions for patentability; non-obvious subject matter
>
> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made . . . ."

Rule 52(a), Federal Rules of Civil Procedure:

> "Findings by the Court
>
> (a) Effect. In all actions tried upon the facts without a jury . . . the court shall find the facts specially and state separately its conclusions of law thereon . . . Findings of fact, whether based on oral or documentary evidence, shall not be set aside unless clearly erroneous, and due regard shall be given to the opportunity of the trial court to judge of [sic] the credibility of the witnesses."

STATEMENT OF THE CASE

Merck, one of America's premier pharmaceutical innovators, is the owner of the '430 patent. That patent describes and claims a pharmaceutical composition comprising as active ingredients 5 milligrams ("mg") of amiloride hydrochloride ("amiloride") and 50 mg of hydrochlorothiazide. The claimed composition (5 mg of amiloride and 50 mg of hydrochlorothiazide) is contained in Merck's prescription medication Moduretic®—a diuretic useful in the treatment of cardiovascular and renal diseases, such as hypertension. Moduretic® resulted from a research and development program involving an estimated 1,000 man-years of effort. Moduretic® is taken by

countless patients each day, as evidenced by the fact that it achieved more than $738,000,000 in worldwide sales during the years 1981-1985 alone.

The Proceedings Below

Seeking FDA approval to market a generic copy of Moduretic®, respondent Biocraft Laboratories, Inc. ("Biocraft") submitted an abbreviated new drug application ("ANDA") to the Food and Drug Administration ("FDA") under Section 505(j) of the Food, Drug and Cosmetic Act, 21 U.S.C. § 355(j). Because it was merely copying Merck's patented and FDA approved formulation, Biocraft was not required to subject its "me-too" copy to the rigors of full-scale clinical testing, but rather was able to rely on the extensive testing and studies previously conducted by Merck. Thus, Biocraft essentially was required to show only that its generic copy was stable and bioequivalent to Merck's Moduretic®.

Because it sought approval to market its generic copy prior to the expiration of Merck's '430 patent, however, Biocraft was required to certify to the FDA that, in Biocraft's view, the '430 patent was invalid. Biocraft's submission of its ANDA, together with its assertion of patent invalidity, constituted an act of infringement of Merck's '430 patent as a matter of law. 35 U.S.C. § 271(e)(2). Consequently, Merck commenced this patent infringement action by filing a Complaint in the United States District Court for the District of New Jersey. Subject matter jurisdiction in the District Court was based on 28 U.S.C. § 1338(a).

Before the District Court, Biocraft asserted two defenses, each of which required Biocraft to bear the burden of proof by clear and convincing evidence—(i) that Merck's '430 patent was invalid for obviousness in view of the prior art under 35 U.S.C. § 103; and (ii) that the '430 patent was unenforceable because of alleged in-

equitable conduct in its procurement from the United States Patent and Trademark Office.

Following a 12-day bench trial, the District Court (Honorable Nicholas H. Politan), in an opinion that carefully analyzed the basic factual inquiries underlying the obviousness issue as set forth by this Court in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966) (*"Graham"*), found that Biocraft had failed to meet its burden as to each of these defenses. Consequently, the District Court enjoined Biocraft from engaging in the commercial manufacture, use and sale of its generic copy of Moduretic® until expiration of the '430 patent.

On appeal, Biocraft dropped its inequitable conduct defense and, as to its obviousness defense, jettisoned virtually all of the prior art presented at trial, relying solely upon a single item of prior art—Merck's own United States Letters Patent No. 3,313,813 ("the '813 patent").[1] The District Court, as its opinion plainly shows, had fully considered all of the evidence presented to it as to the prior art '813 patent, made numerous and detailed findings of fact as to the scope and content of that patent, and concluded that Biocraft had failed to establish that the subject matter of Merck's '430 patent would have been obvious.

In a 2:1 decision, a majority panel of the Federal Circuit reversed. Although the majority declared that "[w]e do not quarrel with the factual findings of the district court" (App. A at 5a) and purported to reverse "as a matter of law," in actuality it disregarded the District Court's key factual findings and *sub silentio* made *de novo* findings of fact in order to reverse. For example, the majority expressly rewrote, indeed reversed, the key

[1] For the convenience of the Court, copies of the '430 patent in suit and the prior art '813 patent have been lodged with the Office of the Clerk of the Supreme Court with the filing of this Petition.

threshold finding of the District Court, erroneously stating:

> "The district court found that the combination of amiloride and hydrochlorothiazide *was disclosed* in the [prior art] '813 patent. 690 F.Supp. at 1383." (App. A at 5a). (Emphasis added).

But, exactly the opposite is true—i.e., the District Court found that the prior art '813 patent did *not* disclose the combination. Indeed, Biocraft had conceded this on appeal:

> "Assessing the correctness of the district court's obviousness ruling requires consideration of two principal issues. First, does a prior art patent, U.S. Patent No. 3,318,813 (the '813 patent), disclose or suggest a combination of amiloride and hydrochlorothiazide? *The court below ruled that it did not*, based primarily on the testimony of Merck's technical expert, deStevens." (Reply Brief for Appellant Biocraft before the Federal Circuit at p. 1). (Emphasis added).

Federal Circuit Judge Bissell, in her strong dissent, recognized the majority's error, stating:

> "The majority opinion incorrectly states that the district court found 'the combination of amiloride and hydrochlorothiazide was disclosed in the '813 patent.' The district court, in fact, found that the '813 patent disclosed 'in excess of 120 pyrazinoylguanidine and 10 possible potassium losing diuretics, [resulting in] more than 1200 possible combinations, of which the combination of Amiloride and Hydrochlorothiazide would be one.' *Id.* The '813 patent does *not* disclose a diuretic composition containing amiloride and hydrochlorothiazide." (App. A at 14a). (Emphasis added).[2]

The majority then ignored other key findings of the District Court and entered *de novo* findings as to other

---

[2] Judge Bissell also dissented from the denial of Merck's Petition for Rehearing.

factual issues by substituting its own view of the evidence for that of the District Court. Specifically, the majority made *de novo* findings that the experimentation which led to the invention of Merck's '430 patent was routine and that the results produced were predictable.

The Long Road To The Invention Of The '430 Patent

Merck's Moduretic®—the specific combination of 5 mg of amiloride and 50 mg of hydrochlorothiazide—is a diuretic agent. Diuretics function by causing the patient to excrete retained fluid and electrolytes, particularly sodium. The excretion of sodium and water helps reduce blood pressure, making diuretics useful in the treatment of hypertension.

Most diuretics, however, have the undesired effect of altering the body's delicate balance of potassium. Excess potassium excretion can result in low blood potassium levels, a condition known as hypokalemia, which is characterized by severe muscular weakness and physical exhaustion. On the other hand, excess potassium retention can result in high blood potassium levels, a condition known as hyperkalemia, which is equally dangerous to the patient.

The invention of the '430 patent is a novel combination of two known diuretics, amiloride and hydrochlorothiazide. Amiloride is a so-called potassium-sparing diuretic—*i.e.*, it minimizes the excretion of potassium. Hydrochlorothiazide, on the other hand, is a potassium-eliminating diuretic which causes the excretion of both potassium and sodium. Merck discovered that the combination of these two diuretics reduced the unwanted potassium loss, while unexpectedly increasing the desirable excretion of sodium.

Claim 3 of the '430 patent is specific to Merck's Moduretic® and Biocraft's generic copy:

> "3. A composition for oral administration which comprises 5 mg. of amiloride hydrochloride and 50 mg. of hydrochlorothiazide."

Merck arrived at the specific formulation of Claim 3 only after extensive research and development effort. As the District Court found, the discovery of new diuretic compositions is a lengthy process requiring "detailed knowledge of chemical compositions and properties and careful scientific experimentation with them to determine their combined effects." (App. B at 28a).

The history of Merck's discovery and development of Moduretic® is characteristic of pharmaceutical research. It began in the late-1950's, when Merck developed chlorothiazide, the first of a large class of orally-active diuretics known as thiazides. Other researchers also worked in this field, most significantly Dr. George deStevens of Ciba-Geigy, who developed hydrochlorothiazide, an improved thiazide-class diuretic. But, as evaluations of the thiazides continued, it became clear that they could cause hypokalemia due to the excessive excretion of potassium.

By late-1959, Merck's Dr. Edward J. Cragoe, Jr., the inventor of the '430 patent, was actively engaged in diuretic research. Over the next several years, Dr. Cragoe led Merck's medicinal chemists in synthesizing a novel class of chemical compounds—known as pyrazinoylguanidines—as part of Merck's diuretic research program. In all, about 1000 different variations were synthesized and tested for potential diuretic activity. While these pyrazinoylguanidines all were somewhat similar in chemical structure, it was discovered that even the most minor structural variation could affect—often dramatically and unpredictably—each compound's impact on sodium excretion, potassium excretion and toxicity.

Merck's prior art '813 patent was filed in October 1962 to cover some of the pyrazinoylguanidines under preliminary investigation at that time. The '813 patent generally discloses a large class of pyrazinoylguanidines,

and over 120 of them, including amiloride, were specifically identified in that patent. The '813 patent also contains additional language which contemplated that any one of this large class of pyrazinoylguanidines could be combined with other diuretics, and listed ten of these other diuretics, including hydrochlorothiazide. The '813 patent generally states that the pyrazinoylguanidines will reduce the excess potassium excretion caused by such other diuretics.

In 1965, years after the discovery of amiloride, Dr. Cragoe directed that amiloride be evaluated in conjunction with hydrochlorothiazide. The resulting combination caused an unexpected increase in sodium excretion, while at the same time maintaining potassium excretion at an acceptable level. Still additional testing led Merck to ultimately select the specific dosage of 5 mg of amiloride and 50 mg of hydrochlorothiazide—Moduretic®—for marketing as a safe and effective medication. At these dosages, amiloride enhances the sodium-excreting effects, but offsets the potassium-losing propensities, of hydrochlorothiazide without causing the body to retain too much potassium. Merck's testing revealed that the onsets and durations of action of amiloride and hydrochlorothiazide were well-matched, permitting once-a-day use of Moduretic®, thereby enhancing patient compliance and insuring that the patient's critical potassium balance was maintained.[3] Moduretic® was approved by the FDA for marketing in the United States in October 1981.

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[3] During the course of its research, Merck also determined by clinical testing that MK-685, another one of the 120 pyrazinoylguanidine compounds disclosed along with amiloride in the prior art '813 patent, although originally thought to be promising, was in fact totally inappropriate for use in a combination product with hydrochlorothiazide.

The District Court Proceedings

A significant portion of the testimony and other evidence presented at trial concentrated on the scope and content of the disclosure of the prior art '813 patent, and what that patent would have meant to a person of ordinary skill in the art back in the relevant time frame of 1965-1966. The District Court, having carefully considered and weighed the technical evidence and the credibility of the witnesses—including the experts—made the basic factual determinations mandated by this Court in *Graham*. Based upon those findings, the District Court concluded that Biocraft had not proven by clear and convincing evidence that the claimed subject matter of the '430 patent as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made. (App. B at 33a, 35a).

A. The District Court Made Findings As To The Persuasiveness And Credibility Of The Expert Witnesses

The District Court made express findings as to the credibility of the various expert witnesses who testified at trial and specifically found the testimony of Merck's expert, Dr. deStevens, to be persuasive as to the scope and content of the '813 patent:

> "In reaching this determination, this Court has heard and considered testimony from various expert witnesses produced by both sides and is satisfied that [Merck's principal expert witness at trial] *Dr. George deStevens*, the inventor of hydrochlorothiazide, *most closely represents the hypothetical person skilled in the art.*" (App. B at 26a-27a). (Emphasis added).
>
> * * *
>
> "Based upon his background and experience, I am satisfied that Dr. deStevens fits this description [of a person of ordinary skill in the art] and, as such, *this Court finds his testimony to be persuasive of the issue of obviousness as it related to the '813 patent.*" (App. B at 28a). (Emphasis added).

B. The District Court Made Findings As To The Scope And Content Of The Prior Art

Biocraft's cornerstone argument was that the '813 patent somehow "highlighted"—and therefore taught (*i.e.*, disclosed)[4]—the specific combination of amiloride and hydrochlorothiazide. The District Court made an express factual finding rejecting that theory:

> "[Biocraft] argues that the combination of amiloride and hydrochlorothiazide are '*highlighted*' and therefore taught by the '813 patent. This Court disagrees." (App. B at 25a n.1).

The District Court also found that the benefits achieved by the invention of the '430 patent were neither described nor even forecast in the prior art '813 patent:

> "Thus, a person skilled in the art, would not be taught by the '813 patent that amiloride and hydrochlorothiazide should be combined to produce the effects as set forth in the '430 patent. *The '813 patent does not* describe or *forecast the effects that the combined drug would have on sodium excretion, potassium excretion and ratio of sodium excretion to potassium excretion.*" (App. B at 29a). (Emphasis added).[5]

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[4] The words "taught" and "disclosed" are synonymous in the patent field. *See Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1579 n.42 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987):

> "Determination of what a patent *teaches* is fact finding, not interpretation. *Graham*, 383 U.S. at 17, 86 S.Ct. at 693, 15 L.Ed.2d at 556, 148 U.S.P.Q. at 467. A patent either *discloses* something or it does not." (Emphasis added).

[5] It is long-settled that unexpected properties of an invention are evidence of nonobviousness. *United States v. Adams*, 383 U.S. 39, 51 (1966); *In re Wright*, 848 F.2d 1216, 1219-20 (Fed. Cir. 1988) (novel properties and unexpected results must be considered); *In re Chupp*, 816 F.2d 643, 645-47 (Fed. Cir. 1987) (unexpected advantageous properties); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986) (unexpected results must be considered), *cert. denied*, 480 U.S. 947 (1987); *In re Lalu*, 747

The Trial Court entered a finding that the '813 patent did no more than broadly contemplate at least ". . . 1200 possible combinations, of which the combination of Amiloride and Hydrochlorothiazide would be one." (App. B at 30a). The Trial Court further found that "there is no indication in the '813 patent as to the preference for amiloride as opposed to any other pyrazinoylguanidine compound, nor hydrochlorothiazide as opposed to other diuretics." (App. B at 30a). And, the District Court also found that there is no "hint" in the '813 patent as to the proportions of amiloride and hydrochlorothiazide recited in Claim 3 and contained in Merck's Moduretic® —*i.e.*, 5 mg of amiloride and 50 mg of hydrochlorothiazide. (App. B at 30a).

F.2d 703, 706-07 (Fed. Cir. 1984) (relevant properties cannot be ignored); *Application of Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977) ("Disregard for the unobviousness of the results of 'obvious to try' experiments disregards the 'invention as a whole' concept of § 103.").

At trial, Merck presented evidence that the '430 invention, including the specific 5 mg/50 mg combination employed in Moduretic®, produces an unexpected increase in sodium excretion. While the District Court did not enter an express finding with respect to that specific combination, when its opinion is fairly read it is clear that the District Court did find that the amiloride/hydrochlorothiazide combination causes increased sodium excretion which could not have been forecast by the '813 patent. For example, the District Court found that Biocraft's now abandoned spironolactone and triamterene prior art, when combined with hydrochlorothiazide, "produce *enhanced sodium excretion* and a potassium saving result, *similar to the results achieved by the '430 patent*, . . ." (App. B at 32a). (Emphasis added). Similarly, in rejecting Biocraft's contention that another item of prior art relied upon by Biocraft at trial (French Medicament Patent No. 2.259M) rendered the '430 invention obvious, the District Court found that the French patent did not "even suggest that amiloride when co-administered with hydrochlorothiazide *would produce the unexpected results actually acknowledged in the '430 patent.*" (App. B at 32a). (Emphasis added).

C. The District Court Made Findings As To The Methodology Of Those Skilled In The Art Of Pharmaceutical Research, As Well As The Complexity And Lack Of Predictability Of Results In The Diuretic Field

The Trial Court made explicit findings as to the manner in which persons skilled in this art select appropriate ingredients for a combination product:

> "The Court rejects [Biocraft's] hypothesis. It oversimplifies the area of expertise necessary to be skilled in the art in this case and, as such, is not persuasive. The methodology for invention in this area is not a helter-skelter combining of 'known diuretic agents.' Rather, detailed knowledge of chemical compositions and properties and careful scientific experimentation with them to determine their combined effects is required. This is not a system of handicapping possible results, but rather, inductive experimentation and research by persons skilled in chemical compounds. It serves no purpose to generalize that the combination of a potassium sparing diuretic with a potassium losing diuretic will produce foreseeable results. One must analyze, synthesize and experiment chemically, pharmacologically, and biologically in order to discover and invent the appropriate combined compound. In hindsight, it is easy to state anyone *could have* achieved the result and combined the compounds. But this is not the test." (App. B at 28a-29a).

When that painstaking research methodology was utilized in the search for new diuretic agents, the District Court, in discussing one of the items of prior art subsequently abandoned by Biocraft on appeal, found that:

> "[A]s expressed by the testimony, a change in one group in a molecule and one atom can completely change the properties and actions of the compound . . . . [T]he mere mention of a whole series of pyrazinoylguanidine[s] does not answer the question of invention. Rather, *depending upon their chemical*

structure, their reaction alone or in combination with other chemicals can be dramatic. In fact, a small difference in medicinal chemistry can make a huge difference in properties, actions and results." (App. B at 33a). (Emphasis added).

Thus, the Trial Court, having heard and considered all the evidence, testimonial as well as documentary, was of the view that based on the disclosures of the prior art '813 patent a person skilled in this art could not have predicted the results that would be achieved by any one of the 1200 possible combinations broadly contemplated by that patent.

D. The District Court Made A Finding Of Fact That The Patented Product Moduretic® Was A Commercial Success

The District Court also found that the uncontroverted evidence of Moduretic®'s commercial success provided additional support for the conclusion that Biocraft had failed to prove obviousness. (App. B at 33a n.4).[6]

E. The District Court, Based On Those Factual Findings, Correctly Concluded That The Invention Was Not Obvious

After making the findings set forth above, the District Court concluded that the prior art '813 patent suggested only that it would have been " 'obvious to try' combining

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[6] Secondary considerations such as commercial success may support the validity of a patent. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Indeed, the Federal Circuit has recognized that objective real-world evidence like commercial success must always be considered and may be the most probative evidence on nonobviousness. *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546 (Fed. Cir. 1984); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1555 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). *See also Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1461 (Fed. Cir. 1984) (commercial success abroad must be considered).

a pyrazinoylguanidine with another potassium losing diuretic" (App. B at 26a), and that the '813 patent would merely "titillate one's desire to experiment." (App. B at 30a). Accordingly, following Federal Circuit precedent, the District Court concluded that the claims of the '430 patent were not proven invalid as obvious. (App. B at 26a).[7]

The Federal Circuit Disregarded The District Court's Findings Of Fact

Stating that it had no "quarrel with the factual findings of the district court," the majority panel reversed on the ground that the Trial Court's holding that obviousness had not been proven was "incorrect as a matter of law," thereby ignoring Rule 52(a) of the Federal Rules of Civil Procedure. (App. A at 5a). The predicate for the Federal Circuit's reversal was not legal error. Rather, the majority directly overturned a key fact finding of the District Court, indirectly set aside numerous other findings, and made several *de novo* findings.

The majority began by turning on its head the District Court's key factual finding that the patented combina-

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[7] The well-established rule that an obvious to try invention is not invalid for obviousness dates back to decisions of the Court of Customs and Patent Appeals ("CCPA"), one of the predecessors of the Federal Circuit. *See In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (rejecting "obvious to experiment" standard); *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1053 (Fed. Cir.), *cert. denied*, 109 S. Ct. 75 (1988); *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987); *American Hosp. Supply Corp. v. Travenol Lab., Inc.*, 745 F.2d 1, 7 (Fed. Cir. 1984); *In re Yates*, 663 F.2d 1054, 1057 (C.C.P.A. 1981); *Application of Goodwin*, 576 F.2d 375, 377 (C.C.P.A. 1978); *Application of Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977) (disregard of results of obvious to try experiments disregards the invention as a whole concept of § 103, and overemphasis on routine nature of data gathering overlooks last sentence of § 103); *Application of Tomlinson*, 363 F.2d 928, 931 (C.C.P.A. 1966).

tion was *not* disclosed in the prior art '813 patent.[8] And, starting from its erroneous springboard, the majority then proceeded to make other *de novo* findings that cannot be reconciled with those of the District Court. For example, contrary to the District Court's findings that the art was unpredictable and did not forecast the results produced by the '430 invention, the majority found that the disclosure of the prior art '813 patent taught a person of ordinary skill in the art that any of the 1200 possible combinations would produce desirable results:

> "[T]he '813 patent instructs the artisan that any of the 1200 disclosed combinations will produce a diuretic formulation with desirable sodium and potassium eliminating properties." (App. A at 6a).[9]

The majority made a further *de novo* finding of fact—again wholly at odds with the District Court's findings—when it found that a person of ordinary skill in the art would have expected the co-administration of amiloride and hydrochlorothiazide to cause more sodium excretion than either diuretic alone:

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[8] Since the majority's reading of the District Court's opinion was incorrect, the first issue that should have been reviewed by the majority, but which was not, was whether the District Court was clearly erroneous in finding that the '813 patent did not disclose the combination of the '430 patent. Here, the District Court correctly determined that the '430 patented combination was neither disclosed nor rendered obvious by the '813 patent. *See United States v. Adams*, 383 U.S. 39, 50 (1966) ("If such a combination is novel, the issue is whether bringing them together as taught by Adams was obvious in light of the prior art.").

[9] This *de novo* finding of fact is also totally at odds with the trial evidence which demonstrated that MK-685, like amiloride one of the pyrazinoylguanidines disclosed in the prior art '813 patent, would not be appropriate for use with hydrochlorothiazide. And, as the CCPA observed as early as 1966, utilization of screening procedures to determine which purportedly obvious compounds will work, and which compounds will not work, can lead to a patentable discovery. *Application of Tomlinson*, 363 F.2d 928, 931 (C.C.P.A. 1966). *See also Application of Cormany*, 407 F.2d 900, 902-04 (C.C.P.A. 1969).

> "Given the prior art teaching that both amiloride and hydrochlorothiazide are natriuretic, it is to be expected that their co-administration would induce more sodium excretion than would either diuretic alone." (Citation omitted). (App. A at 9a).[10]

Finally, while the District Court found no "hint" in the '813 patent as to the proportions for the ingredients recited in the '430 patent, the majority found that the specific dosages and ratio of Claim 3 (and Merck's commercial prescription drug Moduretic®) were arrived at by mere "routine" experimentation. (App. A at 10a).

And, each of the majority's *de novo* findings were entered without even once mentioning, much less applying, the "clearly erroneous" standard of Rule 52(a).

REASONS FOR GRANTING THE PETITION

I. This Court Should Exercise Its Supervisory Authority Over The Federal Circuit To Ensure That It Does Not Engage In *De Novo* Review Of The Basic Factual Inquiries Underlying The Question Of Obviousness As Established By This Court

In the seminal decision regarding 35 U.S.C. § 103, *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), this Court held that:

> "While the ultimate question of patent validity is one of law, *A. & P. Tea Co. v. Supermarket Corp.*, *supra*, at 155, the § 103 condition, which is but one of three conditions, each of which must be satisfied,

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[10] Incredibly, in support of its *de novo* finding the majority cited to a case involving *not* the combination of *diuretics for use in humans, but* the joint use of magnesium oxide and calcium carbide to promote the formation of a nodular structure *in cast iron.* (App. A at 9a).

The majority's *de novo* fact finding is both beyond the proper province of an appellate court and reflects a view of the evidence of the type rejected by the District Court as "hindsighted and result oriented." (App. B at 29a).

> lends itself to several basic factual inquiries. Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or non-obviousness of the subject matter is determined."

More recently, in *Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 811 (1986) (*per curiam*), this Court reaffirmed that the threshold questions relating to obviousness set forth in *Graham* are factual inquiries which are subject to Rule 52(a).

Because the ultimate question of obviousness is regarded as one of law, however, the Federal Circuit, while ostensibly acknowledging that Rule 52(a) is "fully applicable to all findings on which the § 103 issue is decided," *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir.) (on remand from this Court), *cert. denied*, 481 U.S. 1052 (1987), has consistently reviewed trial courts' determinations of the obviousness issue unencumbered by the clearly erroneous standard of Rule 52(a). That is precisely what happened here. In purporting to correct only what it labelled legal error, the majority reviewed and changed the District Court's factual findings in the same fashion that appellate courts review conclusions of law. The Federal Circuit, as it has in the past, simply side-stepped the proper standard of appellate review set forth in Rule 52(a) and mandated by the decisions of this Court. *E.g., Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 810-11 (1986) (*per curiam*), *on remand*, 810 F.2d 1561 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987); *Anderson v. City of Bessemer City, N.C.*, 470 U.S. 564, 573-75 (1985).

The majority embarked upon an independent review of the record and made *de novo* fact findings to justify its reversal of the Trial Court's conclusion. For example, despite the District Court's findings that the testimony

of Dr. deStevens, Merck's expert, was "persuasive of the issue of obviousness as it related to the '813 patent" (App. B at 28a), the majority disregarded that finding and testimony, and made a contrary finding that the '813 patent disclosed the combination of amiloride and hydrochlorothiazide. (App. A at 5a).

Similarly, despite the District Court's finding that the art was unpredictable and that "[i]t serves no purpose to generalize that the combination of a potassium sparing diuretic with a potassium losing diuretic will produce foreseeable results" (App. B at 28a-29a), the majority entered contrary *de novo* findings that it was to be expected that the co-administration of amiloride and hydrochlorothiazide "would induce more sodium excretion than would either diuretic alone." (App. A at 9a).[11] And, despite the District Court's factual finding that the '813 patent did not provide "any hint" as to the ratio or dosages of amiloride and hydrochlorothiazide to be combined, the majority entered a *de novo* finding that "the experimentation needed to arrive at the claimed dosages was nothing more than routine." (App. A at 10a).

The entry of those findings on appeal effectively operated to reverse the Trial Court's findings. The major-

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[11] In finding that Merck's patented combination did not achieve an unexpected increase in sodium excretion, the majority relied in part on the Trial Court's failure to adopt a portion of one of Merck's proposed findings. As this Court has held, however, the failure of a district court to adopt a proposed finding does not constitute a reviewable finding to the contrary—*i.e.*, it does not mean that the Trial Court here found that the specific combination of 5 mg amiloride and 50 mg hydrochlorothiazide did not cause an unexpected increase in sodium excretion. *Kelley v. Southern Pacific Co.*, 419 U.S. 318, 331-32 (1974).

Federal Circuit Judge Bissell, in dissent, correctly recognized that there was no basis for the majority's *de novo* finding:

> "Absent more definitive findings by the district court, the basis for the majority's statement [regarding no unexpected results] escapes me." (App. A at 15a).

ity was wrong to set aside the District Court's findings without first establishing that they were clearly erroneous. Rule 52(a), Fed. R. Civ. P.; *Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 810-11 (1986) (*per curiam*), *on remand*, 810 F.2d 1561 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987); *Anderson v. City of Bessemer City, N.C.*, 470 U.S. 564, 573-75 (1985).[12]

In addition, the majority failed to recognize that Rule 52(a) requires greater deference when findings are based on credibility determinations. *Anderson v. City of Bessemer City, N.C.*, 470 U.S. at 575. Nowhere did the majority pay any deference to the Trial Court's unique opportunity to observe the witnesses and evaluate the evidence, or its determination that Dr. deStevens, Merck's expert, provided the most persuasive testimony regarding the '813 patent. Nor did the majority even attempt to demonstrate that the Trial Court's view of the technical evidence was not permissible. *See Anderson*, 470 U.S. at 573-74 (fact finder's choice between two permissible views of the evidence cannot be clearly erroneous).

The majority was simply not entitled to *sub silentio* ignore—and, indeed, reverse—the findings below apparently because it felt the case should have been decided differently. *Anderson*, 470 U.S. at 573. Yet, that is precisely what happened here.

And, it would appear that this is not the first instance in which the Federal Circuit has disregarded the requirements of Rule 52(a) and the precedents of this Court establishing the proper scope of appellate review and the proper function of the appellate courts. Even after this

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[12] It was also improper for the Federal Circuit to enter *de novo* findings which it apparently considered necessary to resolve the obviousness issue. Under such circumstances, an appellate court, at a minimum, should remand the case to the trial court for further fact finding. *Icicle Seafoods, Inc. v. Worthington*, 475 U.S. 709, 714 (1986); *Pullman-Standard v. Swint*, 456 U.S. 273, 291-93 (1982).

Court's *Panduit* decision, numerous Petitions for Writs of Certiorari have been filed which have charged that the Federal Circuit has either improperly disregarded Rule 52(a), entered *de novo* findings on appeal, or both.[13] Indeed, several Judges have recognized that the clearly erroneous standard has been ignored at the Federal Circuit. *See Ryco, Inc. v. Ag-Bag Corp.*, 857 F.2d 1418, 1433-35 (Fed. Cir. 1988) (dissenting op. by Federal Circuit Judge Nies, dissenting in part); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 319 (Fed. Cir. 1985) (concurring op. by Senior District Judge Harvey); *Jones v. Hardy*, 727 F.2d 1524, 1534 (Fed. Cir. 1984) (dissenting op. by Federal Circuit Judge Kashiwa, dissenting in part).

Most recently, in dissenting from the affirmance of a trial court's setting aside of a jury verdict of nonobviousness, Federal Circuit Judge Newman observed:

> "[T]he panel majority, giving 'full and independent review by the court' to the question of unobviousness, conducts its own analysis of the prior art and draws its independent conclusions, giving no deference whatsoever to the jury verdict. Despite the jury trial, the jury has disappeared from the decisional process."

Newell Companies, Inc. v. Kenney Mfg. Co., 864 F.2d 757, 770 (Fed. Cir. 1988) (dissenting op.), *petition for cert. filed*, No. 88-1936, 58 U.S.L.W. 3014 (July 11, 1989).

The Federal Circuit's decisions have provoked commentators to observe that the Federal Circuit "has adopted the *practice* of supplanting district court factual findings with its own based upon an assertion of legal

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[13] Petitioner is aware of at least 14 Petitions for Writs of Certiorari filed since *Panduit* in which the Federal Circuit has been accused of improperly conducting *de novo* reviews of the trial evidence, entering *de novo* fact findings or otherwise violating Rule 52(a) in patent cases. A list of those cases is reprinted in Appendix D hereto at page 40a.

error . . ." (Emphasis added). *See* Filardi & Scheinfeld, *Appellate Review of Patent Bench Trials: Is The CAFC Following Rule 52(a)?*, in CURRENT DEVELOPMENTS IN PATENT LAW 1985, 9, 26 (Practicing Law Institute, Patents, Copyrights, Trademarks, and Literary Property Course Handbook Series Number 213, 1985). And, the Federal Circuit is most often criticized for "doing *de novo* fact finding and delving into the record on [its] own when [it] should not." Federal Circuit Judge Giles S. Rich, *Thirty Years Of This Judging Business*, 14 AIPLA Q.J. 139, 149 (1986).

Here, as in many cases that have gone before this one, under the guise of correcting only legal error, the majority invaded the fact finding province of the District Court and usurped factual determinations for itself.

The Federal Circuit, like the other circuit courts, should conduct itself in accord with Rule 52(a) and the strictures of proper appellate decision-making. Permitting cases to be retried on appeal inevitably will undermine the authority of the district courts and lead to a multiplicity of appeals. *See* Notes of Advisory Committee on Rules regarding the 1985 amendment to Rule 52(a). It is submitted, therefore, that this Court should exercise its supervisory authority to ensure that the Federal Circuit does not engage in *de novo* review of the findings of fact entered by the trial courts.

II. This Court Should Exercise Its Supervisory Authority To Ensure That 35 U.S.C. § 103 Is Applied So As Not To Conflict With The Patent Clause Of The United States Constitution And Undermine The Painstaking Research Efforts Involved In The Discovery Of New Medicines

Typical of the careful and critically important research necessary in the discovery of a new pharmaceutical drug, Merck's development of Moduretic® was the result of "long toil and experimentation." As the District Court

correctly found, the methodology of invention here involved careful inductive chemical and biological experimentation and research. And, as the Trial Court observed, the research here did not involve predictable results.

In invalidating the '430 patent, the majority ignored these findings and denigrated Merck's research effort as "routine" experimentation which produced nothing more than "predictable" results. Not only was the majority's view at odds with the Trial Court's findings, it ignored the realities of pharmaceutical research. As was the case here, the pharmaceutical researcher frequently works with unpredictable chemical compounds that, while sometimes having closely related chemical structures, can produce drastically different results. By ignoring those realities, the majority has departed from well-established principles of patentability and announced a devastating new precedent that will jeopardize the validity of patents throughout the pharmaceutical industry. That result should not be left uncorrected.

In enacting Section 103, Congress sought to ensure that the manner in which an invention was made would not be determinative of the question of patentability. Thus, the second sentence of Section 103 succinctly provides:

> "Patentability shall not be negatived by the manner in which the invention was made."

As stated in the Revisor's Note to 35 U.S.C. § 103:

> "[I]t is immaterial whether [the invention] resulted from long toil and experimentation or from a flash of genius."

And, this Court has expressly recognized that patentability should not turn on the manner of invention, *Graham v. John Deere Co.*, 383 U.S. at 15-16 and nn.7 & 8, but rather "[t]he emphasis on non-obviousness is one of inquiry, not quality . . ." *Id.*, 383 U.S. at 17. Accordingly, the characterization of an invention as the result of the

use of routine procedures does not negate patentability, but only "begs the question." *Application of Tomlinson*, 363 F.2d 928, 931 (C.C.P.A. 1966). In fact, in 1981 the CCPA expressly disavowed the notion that so-called routine experimentation cannot give rise to a patentable invention:

> "The Solicitor, relying upon *In re Aller*, 42 C.C.P.A. 824, 220 F.2d 454, 105 U.S.P.Q. 233 (1955), argues that it is 'not unobvious to discover optimum or workable ranges by routine experimentation.' In many instances, this may be true. The problem, however, with such 'rules of patentability' (and the ever-lengthening list of exceptions which they engender) is that they tend to becloud the ultimate legal issue—obviousness—and exalt the formal exercise of squeezing new factual situations into preestablished pigeonholes. Additionally, *the emphasis upon routine experimentation is contrary to the last sentence of Section 103.*" (Emphasis added).

In re Yates, 663 F.2d 1054, 1056 n.4 (C.C.P.A. 1981). *See also Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1053 (Fed. Cir.) (equating a "matter of experimentation" test to the often rejected obvious to try standard), *cert. denied*, 109 S. Ct. 75 (1988). Yet, this ill-founded approach was applied by the majority to invalidate the '430 patent here.[14]

Moreover, after having considered the ingredients to be combined, the dosages and ratio of those ingredients, and the results achieved by the combination, the Trial Court expressly found that the '430 invention would only have been obvious to try. As Judge Baldwin recognized in *In re Merck & Co., Inc.*, 800 F.2d 1091, 1100 (Fed. Cir.

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[14] While the majority did make passing reference to the second sentence of Section 103 (App. A at 10a), that reference was mere lip service, for the majority, as part of its effort to rationalize its reversal of the District Court, clearly relied on its *de novo* finding that Merck's procedures were "routine." (App. A at 11a).

1986) (dissenting op.), the failure of the Federal Circuit to reject an obvious to try standard for pharmaceutical patents is highly prejudicial to that industry:

> "The obvious-to-try analysis is an attack on the method of making an invention that specifically penalizes people in areas of endeavor where advances are won only by great effort and expense. The pharmaceutical field is particularly hard hit because there is an overabundance of structures that are obvious to try. . . . Under an obvious to try analysis, any [structure] which ultimately is shown to be effective . . . in human beings would be unpatentable because the researcher dared to follow a logical plan."

Section 103 was enacted by Congress in 1952 to provide uniformity and definiteness to the patent law. *Graham v. John Deere Co.*, 383 U.S. 1, 18 (1966). Indeed, the Federal Circuit was born of the same purpose underlying the enactment of Section 103—"to 'provide national uniformity in patent law.'" *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 109 S. Ct. 971, 983 (1989) (quoting H.R. Rep. No. 97-312, p. 20 (1981)). To achieve that goal, Section 103 must be applied evenly, fairly and across-the-board to all technologies. The majority's decision here undermines that goal.

Merck should not be penalized—and its valuable '430 patent rights should not be terminated—because its invention resulted from a large-scale effort involving systematic research. Careful reasoning, articulated by one of the predecessor courts of the Federal Circuit over 20-years ago, compels the conclusion that finding an invention unpatentable because it claims a composition that was merely obvious to try can only serve to eliminate the incentive to invest in research and development of the type conducted by the pharmaceutical industry that the patent system was designed to foster:

> "Slight reflection suggests, we think, that there is usually an element of 'obviousness to try' in any re-

> search endeavor, that it is not undertaken with complete blindness but rather with some semblance of a chance of success, and that patentability determinations based on that as the test would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of 'research.' "

Application of Tomlinson, 363 F.2d 928, 931 (C.C.P.A. 1966).

Current estimates indicate that the expenditure of approximately $125 million and 10-years of time is required to discover and bring to market a new and useful pharmaceutical product in this country.[15] The Patent Clause of the United States Constitution, Article I, Section 8, Clause 8, provides that the patent system is to serve "[t]o promote the Progress of Science." To achieve that goal, patent protection for inventions which result from the enormous effort required to determine which of countless obvious to try chemical structures, if any, may be valuable medicines appropriate for use in man, should not be nullified by after-the-fact judicial determinations that the extensive research effort was merely "routine", and that the results which were achieved only after years of work were merely "predictable."

The Federal Circuit majority here has construed Section 103 in a manner which will inhibit the discovery of new medicines by denying the patent protection that serves to promote the research necessary to discover those

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[15] These estimates were obtained from the following materials provided by the Pharmaceutical Manufacturers Association, 1100 15th Street, N.W., Washington, D.C. 20005, telephone no. (202) 835-3400: (i) Statement of Gerald J. Mossinghoff, President of the PMA, before the U.S. Senate Special Committee on Aging (July 18, 1989) at p. 6; (ii) *Issue Briefs* (January 1989) at p. 4; and (iii) Wiggins, *The Cost of Developing a New Drug* (June 1987) at pp. iv and 17.

medicines. The majority clearly departed from the express purpose of the Patent Clause of the Constitution and the language of Section 103 by summarily dismissing Merck's costly research and development work as routine and predictable. Because this case potentially has industry-wide impact, this Court should grant Certiorari to clarify the proper application of Section 103 to pharmaceutical patents.

CONCLUSION

For all of the foregoing reasons, Merck's Petition should be granted and a Writ of Certiorari should issue.

Respectfully submitted,

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September 5, 1989

APPENDIX

APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS
FEDERAL CIRCUIT

No. 88-1513

MERCK & CO., INC.,
Plaintiff-Appellee,

v.

BIOCRAFT LABORATORIES, INC.,
Defendant-Appellant.

May 10, 1989

Rehearing Denied June 7, 1989

Joseph M. Fitzpatrick, Fitzpatrick, Cella, Harper & Scinto, New York City, argued, for plaintiff-appellee. With him on the brief, were Nicholas M. Cannella and Lawrence Alaburda. Also on the brief, was John J. Francis, Jr., Shanley & Fisher, P.C., Morristown, N.J., of counsel.

Donald R. Dunner, Finnegan, Henderson, Farabow, Garrett & Dunner, Washington, D.C., argued, for defendant-appellant. With him on the brief, were Robert D. Bajefsky and Carol P. Einaudi. Also on the brief, was Beryl L. Synder, Biocraft Laboratories, Inc., Elmwood Park, N.J., of counsel.

Before BISSELL and MAYER, Circuit Judges, and BENNETT, Senior Circuit Judge.

OPINION

MAYER, Circuit Judge.

Merck & Co., Inc. sued Biocraft Laboratories, Inc. for infringement of its patent, U.S. Patent No. 3,781,430. The United States District Court for the District of New Jersey held that Biocraft failed to show by clear and convincing evidence that the patent was invalid or unenforceable, and enjoined Biocraft from commercially making, using, and selling the claimed diuretic formulations. *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 690 F.Supp. 1376 (D.N.J.1988). Biocraft appeals only the validity aspect of the judgment, arguing that the claimed combinations would have been obvious under 35 U.S.C. § 103. We agree and accordingly reverse the judgment of the district court.

Background

The '430 Patent:

In relevant part, U.S. Patent No. 3,781,430 (the '430 patent), assigned to Merck, claims various "Diuretic Formulations." Inducing diuresis (increased urine excretion) or saluresis (increased electrolyte, particularly sodium, excretion) or both, diuretics are useful in the treatment of cardiovascular and renal diseases. Although the therapeutic effects of diuretics are often lifesaving, many cause hypokalemia, the excessive excretion of potassium ions, a condition manifested by severe muscle weakness and physical exhaustion.

In the formulations claimed in the '430 patent, amiloride hydrochloride (amiloride), a known "potassium conserving" diuretic (induces sodium, but not potassium, excretion), is combined with hydrochlorothiazide, a known

"potassium excreting" diuretic (induces both sodium and potassium excretion). As stated in the specification, the objective of co-administration is to reduce the amount of potassium ions eliminated, without reducing the amount of sodium ions eliminated. The inventor also reports that co-administration results in a "medically . . . synergistic therapeutic accomplishment" because "more sodium ions are eliminated than would be forecast from a knowledge of the natriuretic [sodium excreting] effects of the individual drugs."

The '430 patent contains six claims. The parties agree, however, that all of the claims stand or fall with claims 2 and 3. Claim 1, on which claim 2 depends, and claims 2 and 3 provide as follows:

> 1. A composition for oral administration comprising amiloride hydrochloride and hydrochlorothiazide, wherein the ratio of amiloride hydrochloride to hydrochlorothiazide ranges from about 1:1 to 1:10 by weight of the composition.
>
> 2. A composition according to claim 1 wherein amiloride hydrochloride and hydrochlorothiazide are combined at a ratio of 1 to 10 by weight.
>
> 3. A composition for oral administration which comprises 5 mg. of amiloride hydrochloride and 50 mg. of hydrochlorothiazide.

The Infringement Suit:

Merck's suit against Biocraft was prompted by Biocraft's filing of an abbreviated new drug application (ANDA) with the Food & Drug Administration (FDA) for a generic version of Merck's amiloride/hydrochlorothiazide combination, "Moduretic." The Drug Price Competition and Patent Term Restoration Act of 1984 permits the filing if the generic manufacturer can certify its belief that the patent is invalid or will not be infringed by its proposed manufacture, use or sale of

the drug, and notifies the patent owner of the reasons for its belief. 21 U.S.C. § 355(b)(2)(A)(iv) and (3). However, under 35 U.S.C. § 271(e)(2), the filing is a technical act of infringement, so infringement is not an issue in this case. If a patent owner brings an infringement suit, the FDA cannot approve the ANDA unless the patent is declared invalid or not infringed. 21 U.S.C. § 355(c)(3)(C).

At trial, Biocraft argued that the '430 patent was invalid for obviousness under 35 U.S.C. § 103, and unenforceable because of inequitable conduct. The district court ruled against Biocraft on both counts. Biocraft predicated its section 103 argument on two prior art patents and on prior art relating to spironolactone and triamterene, diuretics that, like amiloride, are potassium conserving. Refreshingly, Biocraft challenges the judgment of the district court only as to obviousness, and restricts its arguments to the teachings of U.S. Patent No. 3,313,813 (the '813 patent), also assigned to Merck.

The '813 patent discloses various (3-amino-5,6-disubstituted-pyrazinoyl) guanidines, one of which is amiloride (claim 11). Per the specification, the claimed compounds are effective diuretic and natriuretic agents. Moreover, the '813 patent teaches that guanidines "selectively enhance the excretion of sodium ions without causing an increase in excretion of potassium ions," and "are useful in combination with other classes of diuretic agents to prevent the loss of potassium which the other diuretics otherwise would cause to be eliminated." Hydrochlorothiazide is identified as an example of a potassium excreting diuretic with which the claimed compounds can be combined.

The '813 patent therefore teaches a genus of which the claims of the '430 patent are a species. The question addressed in the district court was whether the '813 patent taught the specific 1:10/5 mg:50 mg, "medically synergistic," amiloride/hydrochlorothiazide, combination

claimed in the '430 patent. Biocraft argued that the claimed combination was taught because both amiloride and hydrochlorothiazide were highlighted in the '813 patent. Moreover, Biocraft pointed out that the Patent and Trademark Office considered the claimed combination *prima facie* obvious, and allowed the '430 patent only after Merck presented evidence allegedly demonstrating a natriuretic synergism produced by the combination. Asserting that the alleged synergistic effect is not exhibited by the 5 mg:50 mg combination, and that therefore, the effect, even if produced, is not commensurate in scope with the claims, Biocraft argued that neither the purported effect nor the dosage limitations distinguish the claims from the disclosure of the '813 patent. The district court, however, was not persuaded, and held that Biocraft failed to carry its burden of proving the obviousness of the claims. This appeal followed.

Discussion

The district court found that the combination of amiloride and hydrochlorothiazide was disclosed in the '813 patent. 690 F.Supp. at 1383. Further finding that more than 1200 combinations are disclosed, and that neither amiloride nor hydrochlorothiazide are highlighted as preferred embodiments in the '813 patent, however, the district court concluded that the combinations claimed in the '430 patent would merely be "obvious to try," and therefore not barred by 35 U.S.C. § 103. We do not quarrel with the factual findings of the district court, but we believe its conclusion that obviousness had not been proven is incorrect as a matter of law.

An invention is "obvious to try" "where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed.Cir.1988). This is not the situation here. The '813 patent expressly

teaches "that when co-administered with other diuretic agents known to enhance the elimination of potassium ions along with sodium ions, the novel pyrazinoylguanidines of this invention will reduce the excretion of potassium ions and thus overcome this undesirable property of other diuretic agents." As is apparent, "success" is not dependent upon random variation of numerous parameters. On the contrary, the '813 patent instructs the artisan that any of the 1200 disclosed combinations will produce a diuretic formulation with desirable sodium and potassium eliminating properties.

That the '813 patent discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art. *See In re Corkill*, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed.Cir.1985) (obviousness rejection of claims affirmed in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among 'thousands' of compounds"); *In re Susi*, 440 F.2d 442, 445, 169 USPQ 423, 425, 58 CCPA 1074 (1971) (obviousness rejection affirmed where the disclosure of the prior art was "huge, but it undeniably include[d] at least some of the compounds recited in appellant's generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives").

Merck imputes undue significance to the district court's finding that neither amiloride nor hydrochlorothiazide are highlighted in the '813 patent. The description of "specific preferences in connection with a generic formula" is determinative in an analysis of anticipation under 35 U.S.C. § 102. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 279, 49 CCPA 993 (1962); *see also In re Schaumann*, 572 F.2d 312, 315, 316, 197 USPQ 5, 8, 9 (CCPA 1978) ("the disclosure of a chemical genus

. . . constitute[s] a description of a specific compound" within the meaning of section 102(b) where the specific compound falls within the ambit of a "very limited number of compounds"). But in a section 103 inquiry, "the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered." *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA) (1976).

Merck also attributes determinative importance to the district court's finding that the '813 patent does not describe "the effects that the combined drug would have on sodium excretion, potassium excretion and ratio of sodium excretion to potassium excretion" that are described in the specification of the '430 patent, 690 F.Supp. at 1383, nor does it "teach the specific ratios of the combinations" disclosed in the '430 patent, *id.* But, the mere absence from the prior art of a teaching or a limitation recited in the patent at issue is insufficient for a conclusion of nonobviousness. Unlike a section 102 defense which requires that a single reference describe each and every element of a claimed invention, *Structural Rubber Products Co. v. Park Rubber Co.*, 749 F.2d 707, 715, 223 USPQ 1264, 1270 (Fed.Cir.1984), "the question under 35 USC 103 is not merely what the references expressly teach but what they would have suggested to one of ordinary skill in the art at the time the invention was made." *In re Lamberti*, 545 F.2d at 750, 192 USPQ at 280. That this distinction was missed is evident from the district court's erroneous assertion that because the '813 patent " 'suggests,' " but does not " 'teach' " the combinations claimed in the '430 patent, obviousness had not been proven. 690 F.Supp. at 1383.

As prescribed by section 103, the proper focus of an obviousness inquiry is on whether "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

would have been obvious at the time the invention was made to a person having ordinary skill in the art. . . ." Merck argues that the dosages and ratios of claims 2 and 3, and the properties of the 5 mg of amiloride and 50 mg of hydrochlorothiazide combination patentably distinguish the claims of the '430 patent from the teaching of the '813 patent. Relying on evidence allegedly demonstrating that the properties Merck posits are not exhibited by the 5 mg/50 mg combination, Biocraft insists that the claims are invalid under section 103; but this begs the question. Even if Merck's representations are accepted, the issue remains whether the asserted properties and proportions impart patentability to the claimed inventions, or whether the inventions as a whole would have been obvious to one skilled in the art.

Merck offers several theories to bolster the claimed combinations' purportedly nonobvious properties. In response to the examiner's rejection of the claims on the ground that the amiloride/hydrochlorothiazide combination was *prima facie* obvious, Merck said that the coadministration of the two diuretics achieved a "medically synergistic" result. This apparently convinced the examiner, but it should not have.

"The patent law 'allows the inventor to be his own lexicographer,' " *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 867, 228 USPQ 90, 93 (Fed.Cir.1985) (quoting *Autogiro Co. of America v. United States*, 384 F.2d 391, 397, 155 USPQ 697, 702, 181 Ct.Cl. 55 (1976)), but he may not compose his own standards of patentability. Synergism is not a requirement of nonobviousness. *Gardner v. TEC Sys. Inc.*, 725 F.2d 1338, 1349, 220 USPQ 777, 786 (Fed.Cir.1984) (in banc). But when an inventor tries to distinguish his claims from the prior art by introducing evidence of unexpected "synergistic" properties, the evidence should at least demonstrate "an effect greater than the sum of the several effects taken separately." *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282, 96

S.Ct. 1532, 1537, 47 L.Ed.2d 784, 189 USPQ 449, 453 (1976). It is insufficient that, as Merck defines "medical synergism" in the specification of the '430 patent, the "two drugs react favorably."

At trial, Merck altered its approach and tried to show that a greater than additive effect, in terms of sodium excretion, is obtained when amiloride and hydrochlorothiazide are co-administered. It failed. The district court said only that amiloride and hydrochlorothiazide can be co-administered "without a reduction in the amount of sodium ions that are eliminated," 690 F.Supp. at 1378, and that the effect of co-administration as set forth in the specification of the '430 patent was not described in the '813 patent, 690 F.Supp. at 1383. Merck's proposed finding that an unexpectedly strong natriuretic effect occurs was not adopted by the district court. Moreover, on appeal, Merck says only that the evidence at trial "demonstrated that the combination causes more sodium excretion than 50 mg of hydrochlorothiazide alone". This is quite different from the proposition advanced at trial, and imparts no patentability to the claimed inventions.

Given the prior art teaching that both amiloride and hydrochlorothiazide are natriuretic, it is to be expected that their co-administration would induce more sodium excretion than would either diuretic alone. *See In re Crockett*, 279 F.2d 274, 276, 126 USPQ 186, 188, 47 CCPA 1018 (1960) (the "joint use [of magnesium oxide and calcium carbide] is not patentable" where the prior art teaches "that both magnesium oxide and calcium carbide, individually, promote the formation of a nodular structure in cast iron, and it would be natural to suppose that, in combination, they would produce the same effect and would supplement each other"). Indeed, the inventor named on both the '813 and the '430 patents, so testified. When asked: "Isn't it also normal when you administer a potassium sparing compound along with hydrochlorothiazide a period of time, that there would be some increase in the amount of sodium excretion?", he responded:

"That is a possibility. That is not an assured consequence." But, "absolute predictability of success" is not the criterion; "[f]or obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 903, 7 USPQ2d at 1681. When further questioned on the point, the inventor indicated that his uncertainty inhered not in the fact that an increase was to be expected, but only in the magnitude of the increase. This, he testified, "Depends on the amount of potassium sparing compound that you have."

Merck's further contention that the claimed inventions as a whole would not have been obvious because of the recited dosage limitations is equally unpersuasive. "Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235, 42 CCPA 824 (1955). Patentability may be imparted, however, if the results achieved at the designated concentrations are "unexpectedly good." *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977). As discussed above, this is not the situation here. Assuming, as Merck alleges, that "[t]he specific combination of 5 mg of amiloride and 50 mg of hydrochlorothiazide results in no decrease and indeed an increase in sodium excretion over hydrochlorothiazide alone," this was to be expected from the known natriuretic properties of the two diuretics.

The evidence at trial showed that, though requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine. "Patentability shall not be negatived by the manner in which the invention was made." 35 U.S.C. § 103. But the converse is equally true: patentability is not imparted where "the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in

light of the prior art." *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir.1988).

This is precisely the situation here. Merck's expert, the inventor of hydrochlorothiazide, and the witness that the district court found "most closely represents the hypothetical person skilled in the art," 690 F.Supp. at 1382, testified that the dose response and compatability procedures followed by Merck were those that "all pharmaceutical companies [follow] whenever they determine the appropriate dose; the minimal dose and the appropriate dose." After describing the animal and human studies that were conducted, he explained: "That is the way it is done not only with amiloride, but with any other drug that you are testing." Reached by means of routine procedures, and producing only predictable results, the recited dosages therefore do not distinguish the claims of the '430 patent from the amiloride/hydrochlorothiazide combination that the district court properly found was disclosed in the '813 patent. *Cf. United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed.Cir. 1988) (specification is enabling in part because those skilled in the art would know how to conduct a dose response study to determine the appropriate amounts to be used).*

Costs

Biocraft moves to tax Merck the full cost of printing the appendix prepared for this appeal. Biocraft states that Merck disregarded "the spirit, if not the letter, of

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* The district court also referred to evidence of Moduretic's commercial success. Commercial success is an indication of nonobviousness that must be considered in a patentability analysis, *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 693, 15 L.Ed.2d 545, 148 USPQ 459, 467 (1966), but in the circumstances of this case, where it is the only such indication, it is insufficient to render Merck's claimed invention nonobvious. *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1555, 220 USPQ 303, 314 (Fed. Cir. 1983) (objective evidence of nonobviousness "may in a given case be entitled to more weight or less, depending on its nature and its relationship to the merits of the invention").

Fed.Cir.R. 30(b) by citing in its brief portions of the record not specifically relied upon." We agree. Our review of the matter shows, for example, that Merck generally cited hundreds of pages of the record in its preliminary introduction of the witnesses, but relied only on a small fraction of those pages in the remainder of its brief; lengthy scholarly articles were reproduced in their entirety but not relied upon by Merck; and a fully reproduced 700-plus page book, though mentioned once by Merck, was similarly not relied upon.

Accordingly, we grant Biocraft's motion. When assessing costs, the Clerk will tax Merck with the full cost of printing the appendix.

Conclusion

The judgment of the district court is reversed.

REVERSED.

BISSELL, Circuit Judge, dissenting.

I would affirm the district court's decision that the claims at issue in the United States Patent No. 3,781,430 ('430) were not shown to have been obvious under 35 U.S.C. § 103 (1982). The district court concluded that a combination of amiloride and hydrochlorothiazide as claimed in the '430 patent was merely "obvious to try" based on the prior art. *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 690 F.Supp. 1376, 1381 (D.N.J.1988) (citing *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed.Cir.1987) (rejecting "obvious to try" as the standard for determining obviousness)).

Obviousness, a question of law, is based on underlying factual inquiries. *See Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050, 5 USPQ2d 1434, 1438 (Fed. Cir.), *cert. denied*, —— U.S. ——, 109 S.Ct. 75, 102 L.Ed.2d 51 (1988). The parties agree that the closest prior art to the '430 patent is United States Patent No. 3,313,813 ('813). Additionally, the majority opinion *does*

not "quarrel with the factual findings of the district court."

In pertinent part the district court stated:

> The '813 patent discloses appropriately 120 pyrazinoylguanidine compounds. There is no indication in the patent that amiloride is the preferred compound. Thus, a person skilled in the art, would not be taught by the '813 patent that amiloride and hydrochlorothiazide should be combined to produce the effects as set forth in the '430 patent. The '813 patent does not describe or forecast the effects that the combined drug would have on sodium excretion, potassium excretion and ratio of sodium excretion to potassium excretion. A composition must be assessed for obviousness only after consideration of its chemical structure as well as its pharmaceutical and biological properties. In short, while the '813 patent "suggests" exploration of combinations of potassium sparing guanidine with potassium losing diuretics, such as hydrochlorothiazide, it does not "teach" the combinations claims in the '430 patent.
>
> Nor does it teach the specific ratios of the combinations as outlined in Claims 2, 3, 5 and 6 of the '430 patent. Those claims are sufficiently non-obvious so as to sustain the validity of the patent. Since the '813 patent discloses in excess of 120 pyrazinoylguanidine and 10 possible potassium losing diuretics, there are more than 1200 possible combinations, of which the combination of Amiloride and Hydrochlorothiazide would be one. And there is no indication in the '813 patent as to the preference for amiloride as opposed to any other pyrazinolyguanidine compound, nor hydroclorothiozide [sic] as opposed to other diuretics. Nor is there any hint as to the proportions that would be contained in the mixture. Again, while the '813 patent might titillate one's desire to experi-

> ment, it clearly does not teach and thereby make obvious the claims as outlined in Claims 2, 3, 5 and 6 of the '430 patent.

Merck, 690 F.Supp. at 1383-84.

The majority opinion incorrectly states that the district court found "the combination of amiloride and hydrochlorothiazide was disclosed in the '813 patent." The district court, in fact, found that the '813 patent disclosed "in excess of 120 pyrazinoylguanidine and 10 possible potassium losing diuretics, [resulting in] more than 1200 possible combinations, of which the combination of Amiloride and Hydrochlorothiazide would be one." *Id.* The '813 patent does not disclose a diuretic composition containing amiloride and hydrochlorothiazide.

After examining the scope and content of the prior art, the district court found that the '813 patent does not (1) teach one of ordinary skill in the art a preference for amiloride, hydrochlorothiazide, or their combination, (2) "describe or forecast the effects that the combined drug would have on sodium excretion, potassium excretion and ratio of sodium excretion to potassium excretion," and (3) teach the specific ratio limitations of the claims in suit. *Id.* Additionally, the district court determined that the '813 patent only suggests "exploring" combinations of potassium sparing and potassium losing diuretics, and that the prior art does not teach one of ordinary skill what is claimed in the '430 patent. *Id.* I agree. The claimed invention would not have been obvious in view of prior art that does no more than suggest experimenting with over 1200 combinations to come up with the right one.

The meaning to one of ordinary skill in the art of the '813 patent was extensively explored at trial. Based upon this testimony, the district court found that Merck's expert, the inventor of hydrochlorothiazide, "most closely represent[ed] the hypothetical person skilled in the art."

Id. at 1382. After reviewing the prior art, Merck's expert testified that in 1966 the combination of amiloride and hydrochlorothiazide would not have been obvious, and if combined, he would not have expected the results achieved.

In examining secondary considerations, the district court found "uncontroverted evidence" of commercial success, *id.* at 1385 n. 4, but made no express findings on unexpected results. Yet the majority, after extended discussion, finds no unexpected results. Absent more definitive findings by the district court, the basis for the majority's statement escapes me.

Hindsight is not the standard for determining obviousness. *See, e.g., Uniroyal*, 837 F.2d at 1050-51, 5 USPQ2d at 1438. Bits and pieces of the invention claimed in the '430 patent can be pointed to in the prior art, but only if one is armed with hindsight knowledge. *See id.* (stating that hindsight reconstruction using the claimed invention as a blueprint is improper). The majority's opinion does not disturb the district court's factual findings. Based on these findings, I cannot agree with the majority's conclusion that the claims of the '430 patent would have been obvious. Accordingly, I would affirm the district court's judgment.

APPENDIX B

UNITED STATES DISTRICT COURT
D. NEW JERSEY

Civ. A. No. 85-5585

MERCK & CO., INC.,
Plaintiff,

v.

BIOCRAFT LABORATORIES, INC.,
Defendant.

July 11, 1988

John J. Francis, Jr., Shanley & Fisher, Morristown, N.J., Joseph M. Fitzpatrick, Nicholas M. Cannella, Lawrence Alaburda, Salvatore C. Mitri, Fitzpatrick, Cella, Harper & Scinto, New York City, for plaintiff.

Glenn A. Clark, Riker, Danzig, Scherer, Hyland & Perretti, Newark, N.J., Donald R. Dunner, Robert D. Bajefsky, Carol P. Einaudi, Sylvia Blickstein, Legal Asst., Finnegan, Henderson, Farabow, Garrett & Dunner, Washington, D.C., for defendant.

OPINION

POLITAN, District Judge.

Plaintiff, Merck & Co., Inc. ("Merck") is a corporation duly organized and existing under the laws of the State of New Jersey. Merck's principal place of business is at 126 Lincoln Avenue, Rahway, New Jersey. De-

fendant, Biocraft Laboratories, Inc. ("Biocraft") is a corporation duly organized and existing under the laws of the State of Delaware. Biocraft's principal place of business is at 92 Route 46, Elmwood Park, New Jersey. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. § 1338(a). The parties hereto stipulate that each is subject to personal jurisdiction in the United States District Court for the District of New Jersey. Venue is proper in this district by virtue of 28 U.S.C. § 1400(b).

Since its issuance, Merck has been the owner by assignment of the entire right, title and interest in the following United States Letters Patent: Number: 3,781,430 (hereinafter referred to as " '430"), Issue Date: 12/25/73, Expiration Date: 12/24/90, Applicant: Edward J. Cragoe, Jr., Title: Diuretic Formulations. The validity of this patent is the subject matter of this litigation.

Diuretics are valuable therapeutic agents as they are useful in the treatment of cardiovascular and renal diseases. Their use is indicated in the management of all types and grades of severity of congestive heart failure in which diuretic therapy improvement is required. Due to the resulting loss of water and electrolytes, dramatic improvement is noted in peripheral and pulmonary edema, dyspnea, orthopnea, cough, ascites and pleural effusion. Diuretics also provide effective therapy in various forms of renal edema, *e.g.*, edema associated with nephrosis and certain types of nephritis. Their administration results in prompt excretion of retained fluid and electrolytes with consequent benefit to the patient. The desired electrolyte to be excreted is sodium chloride.

Although diuretics are often life-saving because of the above beneficial therapeutic effects, most of them have the disadvantage of causing the excretion of appreciable amounts of potassium ions. When an excessive loss of potassium ions occurs, a severe muscular weakness and feeling of extreme physical exhaustion results.

Merck's '430 patent describes and claims compositions for oral administration comprising combinations of amiloride hydrochloride and hydrochlorothiazide, and methods for the use of such combinations in the treatment of hypokalemia. For ease of reference, both the free base form of amiloride and its hydrochloride salt form (amiloride hydrochloride) will be referred to simply as amiloride. Amiloride is a so-called potassium-sparing diuretic —*i.e.*, it causes the excretion of unwanted sodium without also causing the excretion of potassium. Hydrochlorothiazide, on the other hand, is a so-called potassium-eliminating diuretic, causing both the desired effect of sodium excretion but the undesired effect of potassium loss. The combination of amiloride and hydrochlorothiazide results in a reduction in the amount of potassium ions that are eliminated, without a reduction in the amount of sodium ions that are eliminated.

Claims 1 and 4 of the '430 patent cover, respectively, compositions for oral administration comprising amiloride and hydrochlorothiazide and a method of treating hypokalemia by oral administration of such compositions, wherein the ratio of amiloride to hydrochlorothiazide ranges from about 1:1 to 1:10 by weight. The remaining claims 2, 3, 5 and 6 are specific to Merck's commercial product, which comprises a combination of 5 mg amiloride and 50 mg hydrochlorothiazide and its method of use in treating hypokalemia:

> "2. A composition according to claim 1 wherein amiloride hydrochloride and hydrochlorothiazide are combined at a ratio of 1 to 10 by weight.
>
> 3. A composition for oral administration which comprises 5 mg of amiloride hydrochloride and 50 mg of hydrochlorothiazide.
>
> 5. A method according to claim 4 wherein amiloride hydrochloride and hydrochlorothiazide are at a ratio of 1:10 by weight.

6. A method according to claim 5 which contains 5 mg of amiloride hydrochloride and 50 mg of hydrochlorothiazide."

In October 1981, the Food and Drug Administration ("FDA") approved the marketing of both amiloride alone and also the combination of amiloride and hydrochlorothiazide. Since then, Merck has been marketing and selling in the United States and the European market a commercial product under the brand name *Moduretic* which is a combination of amiloride and hydrochlorothiazide covered by the claims of Merck's '430 patent. *Moduretic* contains 5 mg of amiloride and 50 mg of hydrochlorothiazide, which combination is specifically covered by claims 2 and 3, and its use by claims 5 and 6.

On October 15, 1985, Biocraft submitted an abbreviated new drug application ("ANDA") under § 505(j) of the Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeking approval from the FDA to market a copy of *Moduretic* under a generic name, but likewise containing 5 mg amiloride and 50 mg hydrochlorothiazide. Pursuant to 35 U.S.C. § 271(e)(2), Biocraft's submission of that ANDA constituted an act of infringement of Merck's '430 patent as a matter of law. Thus, infringement is not an issue in this litigation. The only issues in this case are whether Merck's '430 patent is valid and enforceable.

As part of its ANDA, Biocraft asserted that the '430 patent is invalid. As required by statute, on October 15, 1985 Biocraft provided Merck with a statement of the factual and legal bases upon which Biocraft premised its invalidity assertions. Merck thereafter filed the Complaint commencing this patent infringement suit. Biocraft filed its Answer and Counterclaim on December 16, 1985, asserting that the '430 patent was invalid or unenforceable. Merck filed its Reply to Counterclaim on December 24, 1985.

The FDA approved Biocraft's ANDA for a generic copy of *Moduretic* on or about July 15, 1987. The effective date of the FDA's approval of Biocraft's ANDA was April 17, 1988, subject to this Court's power to modify such effective date in accordance with 35 U.S.C. § 355(j)(4)(B)(iii). In the course of the trial, this Court issued an interlocutory injunction restraining Biocraft from marketing its generic copy of *Moduretic* pending final decision in this case.

As hereinbefore indicated, the '430 patent claimed that the combination of amiloride and hydrochlorothiazide produced results supporting the issuance of a patent. Specifically, the '430 patent contains the following statements:

> The invention involves the coadministration of a pyrazinoylguanidine compound with one of the above-mentioned potassium eliminating diuretics to thereby result in a reduction in the amount of potassium ions that are eliminated, without a reduction in the amount of sodium ions that are eliminated. In fact, more sodium ions are eliminated than would be forecast from a knowledge of the natriuretic effects of the individual drugs. The co-administration of these drugs therefore results medically in a synergistic therapeutic accomplishment.
>
> Medically, synergism is obtained when two drugs react favorably. With respect to separate administration of a potassium sparing diuretic and a sodium excreting diuretic, neither of the diuretics can be successfully administered over a period of time without causing undesirable effects on the patient. More specifically, when a sodium excreting diuretic is administered over a period of time, the patient excretes the necessary quantity of undesired Na + (sodium) but in addition thereto excretes the desired K + (potassium), thus subjecting the patient to a hypo-

> kalemia state. When a potassium sparing diuretic is administered separately over a period of time, the patient achieves the desired K + (potassium) balance but the quantity of undesired Na + (sodium) excretion is not obtained. Therefore, the favorable reaction existing between these classes of diuretics is that the potassium sparing diuretic potentiates the natriuretic effect of sodium excreting diuretics while simultaneously reversing the K + (potassium) excretion to the desired positive level.

Before embarking on the sea of invention, certain basic guideposts applicable to this Court's review of the patent in question must be stated.

A patent is enitled to a presumption of validity. 35 U.S.C. § 282; *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 446 (Fed.Cir.1986), *cert. denied*, —— U.S. ——, 108 S.Ct. 85, 98 L.Ed.2d 47 (1987); *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1358-60 (Fed.Cir.), *cert. denied*, 469 U.S. 821, 105 S.Ct. 95, 83 L.Ed.2d 41 (1984), and each individual claim of the patent is presumed valid independent of the validity of the other claims. 35 U.S.C. § 282; *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., supra*, at 446; *Preemption Devices, Inc. v. Minnesota Mining and Mfg. Co.*, 732 F.2d 903, 907 (Fed.Cir. 1984).

When the defense of validity and unenforceability is raised, the defendant bears the burden of proof as to each defense. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569-70 (Fed.Cir.), *cert. denied*, —— U.S. ——, 107 S.Ct. 2187, 95 L.Ed.2d 843 (1987). And that burden requires that the party asserting the invalidity of the patent must do so by clear and convincing evidence. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., supra*, at 446; *American Hoist & Derrick Co. v. Sowa & Sons, Inc., supra*, at 1360. Thus, in the case at

bar, plaintiff need not demonstrate that the '430 patent is valid; rather, plaintiff is entitled to prevail if this Court concludes that defendant has failed to meet its burdens of proof. *Panduit Corp. v. Dennison Mfg. Co.*, *supra*, at 1569-1570; *Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1557 n. 2 (Fed.Cir.), *cert. denied*, 479 U.S. 850, 107 S.Ct. 178, 93 L.Ed.2d 114 (1986). *Jones v. Hardy*, 727 F.2d 1524, 1529 n. 3 (Fed.Cir. 1984); *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 699 n. 9 (Fed.Cir.1983), *cert. denied*, 464 U.S. 1043, 104 S.Ct. 709, 79 L.Ed.2d 173 (1984).

The law is clear that a patent can be obtained only for subject matter which is novel and nonobvious. 35 U.S.C. §§ 101, 102, 103. Obviousness is defined in § 103 in pertinent part as follows:

> A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

While obviousness is a question of law, it is based on factual inquiries concerning the scope and content of the prior art, differences between the prior art and the claims at issue and the level or ordinary skill in the art. Secondary considerations such as commercial success and unexpected results may also be relevant. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S.Ct. 684, 693-94, 15 L.Ed.2d 545 (1966); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1574 (Fed.Cir. 1984). Thus, in the case at bar, a detailed review of the prior art is required to determine the validity of the '430 patent.

All parties agree that the closest prior art to the '430 patent is Cragoe patent #3,313,813 (hereinafter referred to as the '813 patent), which deals generally with pyrazinoylguanidine formulations among which amiloride is one of the covered compounds. Since amiloride is one of the disclosed compounds, defendant argues that the '813 patent's disclosure of amiloride, together with certain other statements made within the patent, constitute the teaching of the prior art which subsumes within it, the claims of the '430 patent. In support of its position, defendant cites specific sections of the '813 patent as follows:

> The compounds of this invention are useful because they possess diuretic and natriuretic properties. They differ from most of the known, effective diuretic agents, however, in that the compounds of this invention selectively enhance the excretion of sodium ions without causing an increase in excretion of potassium ions. The potassium loss, which is caused by known diuretics, often results in a severe muscular weakness. Since the compounds of this invention are essentially free of this potassium depletion, they have this decided advantage as diuretics. As diuretic agents, they can be used for the treatment of edema, hypertension and other diseases known to be responsive to this therapy.
>
> *It has also been found as another feature of this invention that when co-administered with other diuretic agents known to enhance the elimination of potassium ions along with sodium ions, the novel pyrazinoylguanidines of this invention will reduce the excretion of potassium ions and thus overcome this undesirable property of other diuretic agents. The compounds of this invention, therefore, are useful in combination with other classes of diuretic agents to prevent the loss of potassium which the*

other diuretics otherwise would cause to be eliminated. In addition, the compounds of this invention are useful by themselves as diuretic and/or saluretic agents.

* * * *

EXAMPLE 207

Dry filled capsule containing 50 mg. of active ingredient

	Per capsule, mg.
(3,5-diamino-6-chloropyrazinoyl)-guanidine hydrochloride	50
Lactose	273
Magnesium stearate	2
Mixed powders	325

Mix the (3,5-diamino-6-chloropyrazinoyl)-guanidine hydrochloride, from Example 89, lactose, and magnesium stearate and reduce to a No. 60 mesh powder. Encapsulate, filling 325 mg. in each No. 2 capsule.

The above formulations can be employed to prepare compressed tablets or capsules of other novel compounds of this invention hereinbefore described.

It is also contemplated to combine compounds of this invention in unit dosage form with other known diuretic agents, such as, Hydrochlorothiazide, 4'-methyl-6-chlorospiro-[2H-1, 2, 4-benzothiadiazide-3 (4H)-1'-cyclohexane]-7-sulfonamine-1,1-dioxide, trichloromethiazide, cyclopenthiazide, acetazolamine, dichlorphgenamide, chlorthalidone, chlormerodrin, chlorazinil or spironolactone. One example of such a combination is presented below:

EXAMPLE 208

Combination dosage form in dry filled capsule

	Per capsule, mg.
(3-amino-5-isopropylamino-6-chloropyrazinoyl)-3-3-dimethylguanidine huydrochloride (from Example 198)	50
Hydrochlorothiazide	50
Magnesium stearate	2
Lactose	223
Mixed powders	325

(Emphasis supplied)

* * * *

Specifically, the defendant urges that since the '813 patent speaks of the co-administration of a pyrazinoylguandine with other diuretic agents, among which is hydrochlorothiazide, that therefore, what is claimed in the '430 patent is obvious. Defendant further argued that the juxtaposition of the language between Example 207 and 208 highlights[1] the fact that amiloride should be combined with hydrochlorothiazide. The argument is that since Example 207 is a formulation of amiloride, and hydrochlorothiazide is the first diuretic mentioned in the textual statements following that formulation, and since the example 208 formulation contains hydrochlorothiazide (although it does not include amiloride but rather another guanidine) a person of ordinary skill in the art would conclude that the '813 patent teaches that which is claimed in the '430 patent.

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[1] Citing *In re Parameswar Sivaramakrishnan*, 673 F.2d 1383 (C.C.P.A. 1982), defendant argues that the combination of amiloride and hydrochlorothiazide are *"highlighted"* and therefore taught by the 813 patent. This Court disagrees.

It is clear to this Court, and I so find, that while the passages referred to in the '813 patent suggest that it is "obvious to try" combining a pyrazinoylguanidine with another potassium losing diuretic, (one of which is hydrochlorothiazide), it does not teach the unique specific combinations of drugs as outlined in the '430 patent.

It is well settled that "obvious to try" is not the standard for determining obviousness and does not support a conclusion that an invention would have been obvious within the meaning of 35 U.S.C. § 103. *In re Fine*, 837 F.2d 1071, 1075 (Fed.Cir.1988); *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1053 (Fed.Cir.1988); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed.Cir. 1988); *In re Geiger*, 815 F.2d 686, 688 (Fed.Cir.1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed.Cir.1986); *American Hospital Supply Corp. v. Travenol Laboratories, Inc.*, 745 F.2d 1, 7 (Fed. Cir.1984). As stated in *Application of Tomlinson*, 363 F.2d 928, 931 (C.C.P.A.1966):

> Slight reflection suggests, we think, that there is usually an element of 'obviousness to try' in any research endeavor, that it is not undertaken with complete blindness but rather with some semblance of a chance of success, and that patentability determinations based on that as the test would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of "research."

See also, United States v. Ciba-Geigy Corp., 508 F.Supp. 1157, 1167 (D.N.J.1979) ("If this were the standard for obviousness, then the only experiments that would be encouraged by the patent system would be those undertaken blindly and haphazardly.").

In reaching this determination, this Court has heard and considered testimony from various expert witnesses

produced by both sides and is satisfied that Dr. George de Stevens, the inventor of hydrochlorothiazide, most closely represents the hypothetical person skilled in the art. As to this finding concerning "skilled in the art", the Court has carefully considered all of the factors outlined by Judge Markey in *Environmental Designs v. Union Oil Co. of Cal.*, 713 F.2d 693, 696-697 (Fed.Cir. 1983), *cert. denied*, 464 U.S. 1043, 104 S.Ct. 709, 79 L.Ed.2d 173 (1984):

> Factors that may be considered in determining level of ordinary skill in the art include: (1) the education level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) education level of active workers in the field. *Orthopedic Equipment Co., Inc. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376 at 1381-1382 (Fed. Cir.1983). Not all such factors may be present in every case, and one or more of these or other factors may predominate in a particular case. The important consideration lies in the need to adhere to the statute, *i.e.*, to hold that an invention would or would not have been obvious, as a whole, when it was made, *to a person of "ordinary skill in the art"—not to the judge, or to a layman, or to those skilled in remote arts, or to geniuses in the art at hand.* (Emphasis supplied.)

A person of ordinary skill in the art in the 1965 to 1966 time frame (the date of the '430 invention) would have had either a Ph.D. degree in Chemistry or Pharmacology, or an M.D. degree with concentration in medicinal chemistry and renal physiology.[2] Such a person would have

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[2] *See e.g., Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, *cert. denied*, —— U.S. ——, 107 S.Ct. 2187, 95 L.Ed.2d 843 (1987); *Orthopedic Equipment Co. v. United States*, 702 F.2d 1005 (Fed. Cir. 1983).

had several years of hands-on work experience in the design and evaluation of novel diuretic agents and would have been part of a research team that monitored the diuretic activities of novel agents from their first chemical synthesis through, if warranted and appropriate, biological testing first in animals and then in man. That person also would have had personal exposure to structure/activity relationships in a class of potential diuretic compounds, and would have had an understanding of the relationship between animal testing and human trials. Based upon his background and experience, I am satisfied that Dr. de Stevens fits this description and, as such, this Court finds his testimony to be persuasive of the issue of obviousness as it related to the '813 patent.

Defendant asserts that the person "skilled in the art" in this case need not necessarily be a medicinal chemist whose area of expertise is in the preparation, experimentation and testing of new chemical compounds. Rather, defendant argues that it should be a person who uses or tests diuretic agents or has studied the function of the kidney and the modes of action of diuretic agents. Such a person would be a renal physiologist, a pharmacologist, or a physician having a Ph.D. or an M.D., and knowledge of how the kidney functions, the sites and modes of action of diuretics in the kidney and the therapeutic use of these agents. The Court rejects defendant's hypothesis. It oversimplifies the area of expertise necessary to be skilled in the art in this case and, as such, is not persuasive. The methodology for invention in this area is not a helter-skelter combining of "known diuretic agents". Rather, detailed knowledge of chemical compositions and properties and careful scientific experimentation with them to determine their combined effects is required. This is not a system of handicapping possible results, but rather, inductive experimentation and research by persons skilled in chemical compounds. It serves no purpose to generalize that the combination of a potassium sparing diuretic with

a potassium losing diuretic will produce foreseeable results. One must analyze, synthesize and experiment chemically, pharmacologically, and biologically in order to discover and invent the appropriate combined compound. In hindsight, it is easy to state anyone *could have* achieved the result and combined the compounds. But this is not the test. "The test is whether the subject matter of the claimed invention would be obvious to one skilled in the art at the time the inventions were made, *not* what would be obvious to a Judge after reading the patents in suit and hearing the testimony." *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082 (Fed.Cir.1985), *vacated*, 475 U.S. 809, 106 S.Ct. 1578, 89 L.Ed.2d 817 (1986) (failure to explain basis of holding), *aff'd in part*, 810 F.2d 1561 (Fed.Cir.1987), *cert. denied*, —— U.S. ——, 107 S.Ct. 2187, 95 L.Ed.2d 843 (1987). This Court, therefore, rejects the testimony of defendant's expert, Dr. Pruess,[3] as being hindsighted and result oriented without regard to viewing the appropriate "skill in the art" as it existed at the time of the invention.

The '813 patent discloses appropriately 120 pyrazinoylguanidine compounds. There is no indication in the patent that amiloride is the preferred compound. Thus, a person skilled in the art, would not be taught by the '813 patent that amiloride and hydrochlorothiazide should be combined to produce the effects as set forth in the '430 patent. The '813 patent does not describe or forecast the effects that the combined drug would have on sodium excretion, potassium excretion and ratio of sodium excretion to potassium excretion. A composition must be assessed for obviousness only after consideration of its chem-

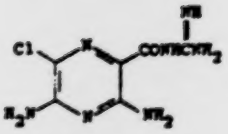
[3] While Dr. Pruess qualified as a renal physiologist who has extensive experience in the clinical use of diuretics, a review of his qualifications shows that he did not have any experience as a researcher involved in the design of medicinal compositions, their structural activity, mechanics of uses or the inductive testing of chemical, pharmocological and/or biological hypotheses created within that process.

ical structure as well as its pharmaceutical and biological properties. In short, while the '813 patent "suggests" exploration of combinations of potassium sparing guanidine with potassium losing diuretics, such as hydrochlorothiazide, it does not "teach" the combinations claims in the '430 patent.

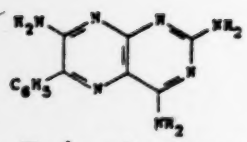
Nor does it teach the specific ratios of the combinations as outlined in Claims 2, 3, 5 and 6 of the '430 patent. Those claims are sufficiently non-obvious so as to sustain the validity of the patent. Since the '813 patent discloses in excess of 120 pyrazinoylguanidine and 10 possible potassium losing diuretics, there are more than 1200 possible combinations, of which the combination of Amiloride and Hydrochlorothiazide would be one. And there is no indication in the '813 patent as to the preference for amiloride as opposed to any other pyrazinoylguanidine compound, nor hydroclorothiazide as opposed to other diuretics. Nor is there any hint as to the proportions that would be contained in the mixture. Again, while the '813 patent might titillate one's desire to experiment, it clearly does not teach and thereby make obvious the claims as outlined in Claims 2, 3, 5 and 6 of the '430 patent.

Defendant also asserts that the prior art regarding spironolactone and triamterene renders the invention described in the '430 patent obvious to one of ordinary skill in the art at the time the invention was made. The evidence shows, and I so find, that amiloride, triamterene and spironolactone have markedly different chemical structures and properties. Because of these differences, one of ordinary skill in the art would have no reasonable basis to expect these compounds to produce similar results, either alone or in combination with hydrochlorothiazide, simply because each was reported to be a potassium-sparing agent.

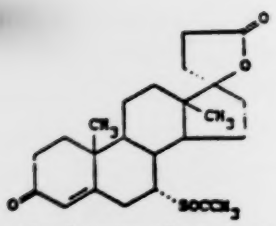
The chemical structures of amiloride, triamterene and spironolactone are as follows:



Amiloride



Triamterene



Spironolactone

As shown above, the chemical structures of spironolactone and amiloride are radically different. Spironolactone possesses a steroid-like structure and belongs to a class of compounds called spirolactones. Because the structural differences between these compounds (amiloride and spirolactone) are so extensive, one of ordinary skill in the art would have had no basis upon which to expect that these compounds, either alone or in combination with hydrochlorothiazide, would produce similar diuretic effects. In addition to structural differences, one of ordinary skill in the art would have understood that the differences in chemical properties between steroidal and non-steroidal compounds would have further precluded any rational expectation that each compound class would produce similar pharmacological effects.

Triamterene, as shown above, is a two-ring structure and belongs to a class of compounds called pteridines. Its chemical structure is significantly different from both spironolactone and amiloride. In addition to differences in structure, amiloride contains a basis guanidine group which is not present in the triamterene molecule. One of ordinary skill in the art would have readily perceived

that amiloride, on the acid-base scale, was a much more basic compound than triamterene, and further understood that this pronounced difference in basicity could have some effect on lipophilicity and ion transport across cell membranes. Due to such chemical and structural differences, there would have been no basis to expect amiloride and triamterene to achieve similar diuretic effects, either alone or in combination with hydrochlorothiazide.

In summary, while both spironolactone and triamterene when combined with hydrocholothiazide produce enhanced sodium excretion and a potassium saving result, similar to the results achieved by the '430 patent, they did not teach, nor even suggest to a person skilled in the art, that the results obtained by the combination as outlined in the '430 patent would occur. It is like comparing apples and oranges. While both are fruits, their creation and chemical compositions are entirely different.

Lastly, defendants assert that the French Medicament Patent constitutes prior art which makes the '430 patent obvious. The French Medicament Patent 2.259M entitled "New Diuretic Medicaments" was issued on January 6, 1964 to Merck. The French patent, like a previously expired U.S. patent 3,268,406 (hereinafter referred to as '406 patent) discloses certain (3-amino-pyrazinoyl) guanidines that possess natriuretic and potassium-sparing properties. The compounds of this patent likewise differ structurally from amiloride in that they do not possess an amino substituent at the 5-position. The French Medicament patent discloses that, when co-administered with other diuretic agents known to increase the elimination of potassium ions, the guanidines of the French patent will reduce the elimination of potassium ions. These disclosures are basically the same as the disclosures of the expired '406 patent. This patent does not, however, even suggest that amiloride when co-administered with hydrocholorothiazide would produce the unexpected results actually acknowledged in the '430 patent. It is a

completely different pyrazinoylguanidine and as expressed by the testimony, a change in one group in a molecule and one atom can completely change the properties and actions of the compound. If anything, the citation of the French Medicament Patent shows that the mere mention of a whole series of pyrazinoylguanidine does not answer the question of invention. Rather, depending upon their chemical structure, their reaction alone or in combination with other chemicals can be dramatic. In fact, a small difference in medicinal chemistry can make a huge difference in properties, actions and results.

Accordingly, this Court has concluded, after reviewing all the prior art, that the '430 patent was not obvious under the applicable legal standards.[4]

The second prong to defendants attack on the '430 patent is that the plaintiff has been guilty of inequitable conduct before the patent office and, therefore, should be barred from enforcing the patent in the case at bar. The applicable standard for this Court to assess inequitable conduct is set forth in *N.V. Akzo v. E.I. DuPont de Nemours*, 810 F.2d 1148, 1153 (Fed.Cir.1987):

> The defense of inequitable conduct requires proof of (1) an act of misrepresentation, (2) which was material, (3) involving information that was known or should have been known to the patentee, and (4) which was committed with the requisite intent. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed.Cir.1983), *cert. denied*, 464 U.S. 1043, 104 S.Ct. 709, 79 L.Ed. 2d 173 (1984). *See also J.P. Stevens & Co. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 223 U.S.P.Q. 1089 (Fed.Cir.1984), *cert. denied*, [474] U.S. [822], 106 S.Ct. 73, 88 L.Ed.2d 60 (1985).

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[4] The court also notes the uncontroverted evidence of *Moduretic's* commercial success as providing additional support for the finding that defendant has failed to sustain its burden of proof as to obviousness.

> The elements of materiality and intent must be determined separately and then weighed together to ascertain whether the patentee engaged in inequitable conduct. The tribunal must then carefully balance the materiality and intent: the less material the proffered or withheld information, the greater the degree of intent that must be proven. In contrast, a lesser degree of intent must be proven when the information has a great degree of materiality. Indeed, gross negligence can be the intended level of intent when the misrepresentation has a high degree of materiality. Simple negligence, however, or an error in judgment is never sufficient for a holding of inequitable conduct. *J.P. Stevens & Co.*, 747 F.2d at 1560, 223 U.S.P.Q. at 1092; *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1363, 220 U.S.P.Q. 763, 777 (Fed.Cir.), *cert. denied*, 469 U.S. 821, 105 S.Ct. 95, 83 L.Ed.2d 41 (1984).

As to this claim, defendants also carry the burden of proof by clear and convincing evidence, with respect to its charges of inequitable conduct. *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 (Fed.Cir.1987); *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698 (Fed.Cir.1983), *cert. denied*, 464 U.S. 1043, 104 S.Ct. 709, 79 L.Ed.2d 173 (1984).

Defendants basic attack upon the plaintiff in this regard is that the prior art concerning spironolactone, triamterene, and French Medicament Patent were not disclosed to the P.T.O. examiner and, therefore, plaintiff was guilty of inequitable conduct. As heretofore expressed in this opinion, it is this Court's finding that those three items of prior art do not bear any chemical or structural relationship to the invention disclosed by the '430 patent. The mere fact that the results obtained by those formulations are similar to the '430 patent is simplistic and does not answer the basic question of obviousness or materiality. They are chemically and structurally dissimilar. Knowledge of their chemical proper-

ties or combined results with hydrochlorothiazide would not, in any way, be material to the claims of the '430 patent and therefore would not have been material to the PTO examiner. Moreover, as indicated in the record, the '813 patent (admitted by all parties to be the closest prior art to the '430 patent) was before the examiner who clearly assessed its possible applicability to the '430 patent application, and held it not to be preclusive prior art. In addition to its lack of materiality, there is absolutely nothing in this record before the Court to state or suggest in any degree that there was an intent to mislead the P.T.O. examiner.

This Court has thoroughly reviewed all of the actions and entire procedural history before the Patent Office and finds no inequitable conduct or intent to mislead or act fraudulently in connection with plaintiff's actions before the Patent Office. I find no inequitable conduct shown or convincing evidence of threshold levels of materiality and wrongful intent. *J.P. Stevens & Co. v. Lex Tex, Ltd.*, 747 F.2d 1553, 1561 (Fed.Cir. 1984), *cert. denied*, 474 U.S. 822, 106 S.Ct. 73, 88 L.Ed.2d 60 (1985).

Based upon my review and examination of the exhaustive record before me, I am satisfied that defendant has not sustained its burden of proof by clear and convincing evidence that the '430 Patent is invalid and/or that the inventor was guilty of inequitable conduct before the Patent Office. Accordingly, judgment will be entered in favor of the plaintiff and against the defendant on both the Complaint and Counterclaim. Pursuant to 35 U.S.C. § 271, this Court shall also provide in its judgment that the effective date of the FDA approval of defendant Biocraft's ANDA for generic *Moduretic* shall be December 24, 1990, and that Biocraft is enjoined from engaging in the commercial manufacture, use and sale of generic *Moduretic* until December 24, 1990.

The foregoing shall constitute my findings of fact and conclusions of law.

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Civil Action No. 85-5585

HON. NICHOLAS H. POLITAN

U.S.D.J.

MERCK & CO., INC.,

Plaintiff,

v.

BIOCRAFT LABORATORIES, INC.,

Defendant.

FINAL JUDGMENT

For the reasons expressed in this Court's Opinion dated July 11, 1988, it is

ORDERED AND ADJUDGED as follows:

1. Judgment is entered in favor of the plaintiff and against the defendant on the Complaint;

2. Judgment is entered in favor of plaintiff and against the defendant dismissing the Counterclaim;

3. The effective date of the FDA approval of defendant Biocraft Laboratories, Inc.'s ANDA for generic *Moduretic*, shall be December 24, 1990;

4. Defendant Biocraft Laboratories, Inc. be and it is hereby enjoined from engaging in the commercial manufacture, use and sale of generic *Moduretic* until December 24, 1990.

/s/ Nicholas H. Politan
NICHOLAS H. POLITAN
U.S.D.J.

DATED: July 11, 1988.

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

88-1513

MERCK & CO., INC.,
Plaintiff-Appellee,

v.

BIOCRAFT LABORATORIES, INC.,
Defendant-Appellant.

On Appeal from the United States District Court
for the District of New Jersey
in Case No(s). 85-5585

JUDGMENT

This CAUSE having been heard and considered, it is ORDERED and ADJUDGED:

REVERSED.

ENTERED BY ORDER OF THE
COURT

/s/ Francis X. Gindhart
FRANCIS X. GINDHART
Clerk

Dated: May 10, 1989

Issued as a Mandate: June 21, 1989
Costs: Against Appellee
Printing $5,684.79
TOTAL $5,684.79

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

88-1513

MERCK & CO., INC.,
Plaintiff-Appellee,

v.

BIOCRAFT LABORATORIES, INC.,
Defendant-Appellant.

ORDER

Before BISSELL, Circuit Judge, BENNETT, Senior Circuit Judge, and MAYER, Circuit Judge.

A petition for rehearing having been filed in this case,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for rehearing be, and the same hereby is, denied.

Circuit Judge Jean Galloway Bissell would grant the petition.

The suggestion for rehearing in banc is under consideration.

The mandate will issue on June 14, 1989.

FOR THE COURT

/s/ Francis X. Gindhart
FRANCIS X. GINDHART
Clerk

June 7, 1989

cc: Donald R. Dunner
Joseph M. Fitzpatrick

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

88-1513

MERCK & CO., INC.,
Plaintiff-Appellee,

v.

BIOCRAFT LABORATORIES, INC.,
Defendant-Appellant.

ORDER

A suggestion for rehearing in banc having been filed in this case, and a response thereto having been invited by the court and filed,

UPON CONSIDERATION THEREOF, it is

ORDERED that the suggestion for rehearing in banc be, and the same hereby is, declined.

FOR THE COURT

/s/ Francis X. Gindhart
FRANCIS X. GINDHART
Clerk

Dated: July 3, 1989

cc: Donald R. Dunner
Joseph M. Fitzpatrick

APPENDIX D

Petitions For Writs Of Certiorari
Since *Panduit* That Have Raised Issues
Regarding The Proper Scope Of Appellate Review

1. *Daig Corp. v. Medtronic, Inc.*, 479 U.S. 931 (1986) (*cert. denied*).
2. *CBS Inc. v. Moleculon Research Corp.*, 479 U.S. 1030 (1987) (*cert. denied*).
3. *Stora Kopparbergs Bergslags AB v. Crucible, Inc.*, 479 U.S. 1034 (1987) (*cert. denied*).
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No. 89-368

IN THE

Supreme Court of the United States

OCTOBER TERM, 1989

MERCK & CO., INC.,

Petitioner,

v.

BIOCRAFT LABORATORIES, INC.,

Respondent.

ON PETITION FOR WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF IN OPPOSITION OF RESPONDENT BIOCRAFT LABORATORIES, INC. TO PETITION FOR WRIT OF CERTIORARI

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STATEMENT PURSUANT TO RULE 28.1

The subsidiaries (except wholly-owned subsidiaries) and affiliates of Respondent Biocraft Laboratories, Inc., are as follows:

None

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I. INTRODUCTION

In its Petition, Merck portrays the Federal Circuit as a runaway court that disregarded the clearly erroneous standard of Fed. R. Civ. P. 52(a) in reversing the district court decision, ignored the findings of the district court, wrote new findings, and deviated from its own precedents as well as those of this Court in reaching the legal conclusion that U.S. Patent No. 3,781,430, Merck's patent in suit (the '430 patent), was invalid. Incredibly, it contends that the Federal

Circuit's actions in this case will adversely impact on future pharmaceutical research. The Federal Circuit, however, was guilty of none of these sins. It accepted the relevant findings of the district court. Thus, the clearly erroneous standard of Rule 52(a) is not an issue. Not a single relevant finding of the district court was ignored and no new findings were written. Moreover, the decision is fully consistent with the decisions of this Court and the Federal Circuit's prior precedents. It will have no discernible impact on pharmaceutical research. In short, the Petition is full of rhetoric but little substance. It should be denied.

II. STATEMENT OF THE CASE

Merck has attempted to portray the development of Moduretic® as long and arduous, and characteristic of pharmaceutical research. (Petition at 8-9.) Merck's history, however, presents a distorted picture. It relies on work performed at Merck during the late 1950's and early 1960's, all of which is irrelevant since the prior art reference upon which the Federal Circuit's invalidity holding is based became available in 1964. *Cf. Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (unsuccessful attempts to reach a solution to problem solved by invention occurring before availability of prior art are "wholly irrelevant"). As will be demonstrated below, this single prior art reference taught combining the two compounds found in the composition claimed in the '430 patent for the very same purpose as they are combined in the '430 patent. In fact, the district court found that the composition claimed in the '430 patent achieved precisely the results taught by the prior art reference.

The facts found by the district court in this case thus present a more compelling case of obviousness

then was found in *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 281-82 (1976), and *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), wherein this Court held that a combination of old elements is unpatentable if each of the elements performs its known function and the combination does not achieve an unexpected result. Consequently, the Federal Circuit's reversal of the district court's validity determination was legally sound. Those prior precedents are particularly compelling here because the prior art patent was owned by Merck and provided Merck with 17 years of patent protection for the very same subject matter that is covered by the '430 patent. Thus, we are here faced with a situation where Merck is attempting to extend the period of exclusivity by obtaining two patents for one patentable invention.

The genesis of the subject matter of the '430 patent is a discovery by Merck's scientists that a group of pyrazinoylguanidines, one of which was amiloride, had beneficial diuretic properties that caused the urinary excretion of sodium, but not potassium, and when coadministered with certain other diuretics, such as hydrochlorothiazide, prevented the undesirable loss of potassium caused by these other diuretics. These pyrazinoylguanidines, including amiloride, were disclosed and claimed in prior art U.S. Patent No. 3,313,813 (the '813 patent).[1] The disclosure of the prior art '813 patent, which became available in 1964, expressly taught that each of the disclosed pyrazinoylguanidines would cause sodium excretion without also causing potassium excretion and that each pyrazinoylguanidine would prevent the loss of potassium caused by

[1] Merck submitted copies of the '813 patent to the Court at the time it filed its Petition.

a potassium losing diuretic. (Col. 3, ll. 10-22.) The patent expressly identified amiloride as a pyrazinoylguanidine and hydrochlorothiazide as a potassium-losing diuretic. (Col. 49, Examples 207 and 208.)

The '430 patent claims a combination of amiloride and hydrochlorothiazide in specified ratios or amounts. The patent itself alleges that the combination of amiloride and hydrochlorothiazide produced the unexpected result of causing more sodium excretion than would have been expected from the sodium excreting properties of the individual compounds. Indeed, it was this allegation—which the district court found was incorrect with respect to the specific combination patented—that induced the Patent and Trademark Office (PTO) to grant the '430 patent. More specifically, while the applications leading to the '430 patent were before the PTO, they were rejected as obvious over the '813 patent. The '430 patent issued *only* after Merck submitted evidence which allegedly demonstrated that the combination produced an unexpected level of sodium excretion in animal and human studies.

Merck, however, did not disclose to the PTO that its scientists had concluded, after years of testing, that the alleged unexpected increase in sodium excretion was obtained only when the amount of amiloride was so high that it caused the retention of too much potassium and was therefore unsafe. As the testimony of Merck's Medical Director in charge of the clinical testing of the amiloride-hydrochlorothiazide combination established, those scientists had concluded that a meaningful increase in the sodium excretion was not obtained when 5 mg. of amiloride was co-administered with 50 mg. of hydrochlorothia-

zide. (App. E at 6a-14a.) That evidence is significant because that is the composition that both Merck and Biocraft sell and which is covered by every one of the '430 patent claims.

The district court found that the combination of amiloride and hydrochlorothiazide was one of approximately 1,200 combinations of a pyrazinoylguanidine and a potassium-losing diuretic disclosed in the '813 patent, but that neither amiloride nor hydrochlorothiazide was indicated to be preferred. (App. B at 30a.) It further found that the '813 patent did not suggest the properties which the '430 patent *alleged* were obtained by the amiloride-hydrochlorothiazide combination. (App. B at 29a.) It therefore held that the claimed composition was merely obvious to try (App. B at 26a), *even though it also found that the claimed composition of 5 mg. amiloride and 50 mg. of hydrochlorothiazide merely achieved the results described in the prior art '813 patent and not the unexpected property described in the '430 patent*, that is, it merely caused a decrease in potassium excretion, without also causing a decrease in sodium excretion. (App. B at 18a.)

In the decision attacked by Merck, the Federal Circuit found that the district court committed an error of law. It ruled that, when the teachings of the '813 patent, as found by the district court, are considered in conjunction with the properties *actually achieved* by the claimed composition (as opposed to those *alleged* in the '430 patent), the claimed invention would have been obvious to a person of ordinary skill in the art and not, as the district court found, merely obvious to try. That holding was fully consistent with the prior precedents of this Court and was based upon

the factual findings actually made by the district court. As will be demonstrated below, that decision did not violate Rule 52(a). As a result, there is no need for this Court to exercise its supervisory authority and grant certiorari to review this case.

III. THERE IS NO NEED FOR THIS COURT TO EXERCISE SUPERVISORY AUTHORITY OVER THE FEDERAL CIRCUIT IN THIS CASE

The rules of this Court provide that review by way of writ of certiorari "will be granted only when there are special and important reasons therefor." (Rule 17.1.) Merck asserts that this Court should exercise its supervisory authority over the Federal Circuit to ensure (1) compliance with Rule 52(a), Fed. R. Civ. P., in reviewing obviousness determinations made by the district courts, and (2) that 35 U.S.C. § 103 is applied in a manner which does not undermine pharmaceutical research. (Petition at 17-27.) Given the facts of this case, neither reason meets the criteria of Rule 17.1.

As will be demonstrated below, the Federal Circuit has adopted an analytical technique in determining the legal question of obviousness which recognizes that the factual inquiries underlying that legal conclusion must be considered under the clearly erroneous standard of Rule 52(a). Moreover, in this case, Rule 52(a) is not even implicated since the Federal Circuit accepted all the factual findings of the district court and did not, as Merck alleges, engage in a de novo review of those facts. It will also be shown that it is absurd for Merck to assert, as it does in its Petition, that Federal Circuit decisions are somehow undermining research efforts in the pharmaceutical or any other industry.

A. The Federal Circuit Has Adopted The Correct Analytical Technique In Reviewing District Court Determinations Of The Legal Question Of Obviousness And The Underlying Factual Findings That Must Be Made To Resolve That Question

Merck is not the first petitioner to contend that the Federal Circuit has failed to adhere to the clearly erroneous standard of Rule 52(a). Indeed, that is the common complaint of many petitioners who are dissatisfied with the decisions of the Courts of Appeals.[2]

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[2] In an effort to support is assertion that the Federal Circuit disregards the mandate of Rule 52(a), Merck cites fourteen petitions for certiorari, all of which have been denied, in which petitioners alleged that the court had violated Rule 52(a). Those citations merely demonstrate that the losing party will often complain that the appellate court failed to adhere to the clearly erroneous requirement. This is amply demonstrated by the fact that at least nine petitions for certiorari from the Second Circuit were filed during the same period and make similar allegations. *Atlantic Richfield Co. v. Interstate Oil Transport Co.*, 479 U.S. 817 (1986) (*cert. denied*); *Joseph J. Santacroce, Sheriff of Nassau County v. Herbert Badgley*, 479 U.S. 1067 (1987) (*cert. denied*); *County of Suffolk v. Arthur V. Graseck, Jr.*, 480 U.S. 918 (1987) (*cert. denied*); *Brenda Berkman v. City of New York*, ___ U.S. ___, 108 S. Ct. 146 (1987) (*cert. denied*); *Shoe World, Inc. v. El Greco Leather Products Co.*, ___ U.S. ___, 108 S. Ct. 71 (1987) (*cert. denied*); *Insurance Co. of North America v. Globe Tankers*, ___ U.S. ___, 108 S. Ct. 454 (1987) (*cert. denied*); *Vladimir Sokolov v. United States*, ___ U.S. ___, 108 S. Ct. 1728 (1988) (*cert. denied*); *Gerda Dorothea Deweerth v. Edith Marks* Baldinger, ___ U.S. ___, 108 S. Ct. 2823 (1988) (*cert. denied*); *Leonard M. Freeman v. Heidi Weissmann*, 58 U.S.L.W. 3219 (U.S. Oct. 2, 1989) (No. 89-114) (*cert. denied*). Significantly, in *Insurance Co. of North America*, the petitioner urged, in language strikingly similar to Merck's:

> The court of appeals decision in this case is yet another instance of the Second Circuit's practice of

This Court has already granted a petition for certiorari to address a contention that the Federal Circuit ignored Rule 52(a) "in substituting its view of factual issues for that of the District Court." *Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 810 (1986). In granting that petition, this Court summarily vacated the Federal Circuit's judgment and remanded the case to that court, stating:

> The Federal Circuit . . . did not mention Rule 52(a), did not explicitly apply the clearly-erroneous standard to any of the District Court's findings on obviousness, and did not explain why, if it was of that view, Rule 52(a) had no applicability to this issue. We therefore lack an adequate explanation of the basis

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exceeding its authority under Rule 52 of the Federal Rules of Civil Procedure by disregarding the trial court's findings of facts. [Petition at 5.]

Similarly, Merck's reliance on four dissenting or concurring opinions and two publications which allegedly complained that the Federal Circuit engaged in fact finding does not justify granting certiorari. Similar dissents and articles can no doubt be found in every circuit. Moreover, two of the four opinions have no bearing on the issue presented by Merck. In *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309 (Fed. Cir. 1985), the concurring opinion did not even suggest that the Federal Circuit had not abided by Rule 52(a). To the contrary, the writer stated: "I agree with the majority that the findings of fact in this case withstand scrutiny under such [clearly erroneous] standard of review." 776 F.2d at 319. In *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757 (Fed. Cir. 1988), *cert. denied*, 58 U.S.L.W. 3213 (U.S. Oct. 2, 1989) (No. 88-1936), the appeal was from a jury verdict and thus Rule 52(a) was not in issue. In fact, Judge Newman, in dissent, expressly stated that the majority's analytic technique would have been appropriate in a bench trial because of the applicability of Rule 52(a). 864 F.2d at 781.

> for the Court of Appeals' judgment: most importantly, we lack the benefit of the Federal Circuit's informed opinion on the complex issue of the degree to which the obviousness determination is one of fact.

475 U.S. at 811.

On remand, the Federal Circuit clearly articulated the interplay of fact and law in the obviousness determination and the applicability of the clearly erroneous standard to that analysis. The court stated:

> On review of a judgment based on a conclusion of obviousness under 35 U.S.C. § 103, this court must consider not only whether there is legal error, but also whether the underlying findings are either nonprobative, or clearly erroneous, or both. If, unlike the present case, a district court had not made findings necessary to resolution of the § 103 question, and legal error were present, an appellate court would vacate in view of that legal error and remand for the district court to make the missing findings. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 872-75, 228 USPQ 90, 97-99 (Fed. Cir. 1985). If unassailable findings were made but could not support the appealed judgment under a proper application of law, an appellate court may vacate or reverse but not make its own findings. *Icicle Seafoods, Inc. v. Worthington*, U.S. ___, ___, 106 S.Ct. 1527, 1530, 89 L.Ed.2d 739, 743 (1986).
>
> . . . .

> To obtain reversal without remand, an appellant-patentee must convince this court that the patent challenger failed at trial to carry its statutory burden, 35 U.S.C. § 282, of proving by clear and convincing evidence sufficient facts to support the obviousness conclusion. One way to do that is to show that a proper application of the law to unassailable findings compels reversal. Another is to show that the findings on which the obviousness conclusion rested are clearly erroneous and that nothing of record warrants a further exercise of the fact-finding function or indicates any possibility that the appealed judgment might be sustained by such exercise.

Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1565-66 (Fed. Cir. 1987), footnotes omitted.

This Court, apparently satisfied with this analysis, denied certiorari of the Federal Circuit's remand decision. *Dennison Mfg. Co. v. Panduit Corp.*, 481 U.S. 1052 (1987).

Indeed, the analysis is fully consistent with the following guidelines set forth in *Icicle Seafoods, Inc. v. Worthington*, 475 U.S. 709, 714 (1986):

> If the Court of Appeals believed that the District Court had failed to make findings of fact essential to a proper resolution of the legal question, it should have remanded to the District Court to make those findings. If it was of the view that the findings of the District Court were "clearly erroneous" within the meaning of Rule 52(a), it could have set them aside on that basis. If it be-

> lieved that the District Court's factual findings were unassailable, but that the proper rule of law was misapplied to those findings, it could have reversed the District Court's judgment.

The Federal Circuit had recognized, prior to the *Panduit* remand decision, that while the conclusion of obviousness is a matter of law, the correctness of the factual findings upon which that legal conclusion is based must be reviewed under the clearly erroneous standard of Rule 52(a). *See Lear Siegler, Inc. v. Aeroquip Corp.*, 733 F.2d 881, 887 (Fed. Cir. 1984); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 313 (Fed. Cir. 1985). It has adhered to that standard after the *Panduit* remand. *See Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050 (Fed. Cir.), *cert. denied*, ___ U.S. ___, 109 S. Ct. 75 (1988); *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 989 (Fed. Cir. 1988); *Ryco, Inc. v. Ag-Bag Corp.*, 857 F.2d 1418, 1423 (Fed. Cir. 1988); *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 886 (Fed. Cir. 1988).

In this case, the Federal Circuit adhered to that analytical technique. It accepted the findings of the district court, but reversed because the proper rule of law was misapplied to those findings.

B. The Federal Circuit's Decisions Do Not Conflict With The Patent Laws Nor Undermine Pharmaceutical Research

It is difficult to believe that Merck can seriously charge that the decisions of the Federal Circuit are somehow inconsistent with the patent laws and may undermine pharmaceutical research. After all, it is well recognized in both the legal and lay communities

that the Federal Circuit has had a positive impact on the value of patents. *See* Sobel, *The Court of Appeals for the Federal Circuit: A Fifth Anniversary Look at its Impact on Patent Law and Litigation*, 37 Am. Univ. L. Rev. 1087, 1089-92 (1988) ("a climate more favorable to upholding the validity and particularly the non-obviousness of patents has emerged"; "the court has brought about a philosophical change which strengthens the patent system."); Dwyer, *Legal Affairs*, Bus. Wk., May 22, 1989, at 78, 79; Moskowitz, *Technology Owners' Ace in the Hole*, Chem. Wk., Mar. 4, 1987, at 22, 23-24; Gabor, *Breakthroughs May Occur in Labs, but Biotech Money is Made in Court; Fighting Over Splice of Life*, U.S. News & World Report, Nov. 24, 1986, at 52; Perry, *The Surprising New Power of Patents*, Fortune, June 23, 1986, at 57, 60.

With specific reference to the pharmaceutical industry, the Federal Circuit has not hesitated to uphold patents in the pharmaceutically related areas. See *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987), *SmithKline Diagnostics, supra.*

Moreover, the decision below provides no disincentive for pharmaceutical research. Merck's research efforts which led to the discovery of amiloride and its use in combination with hydrochlorothiazide were fully rewarded by the grant of the '813 patent. The Federal Circuit ruling in this case is thus quite narrow. It merely holds that, given the teachings of the '813 patent that numerous compositions, including one composed of amiloride and hydrochlorothiazide, have desirable diuretic properties, a second patent covering a composition of amiloride and hydrochlorothiazide

cannot be obtained unless the combination produces unexpected results. That has long been the law.[3] Thus, Merck's suggestion that the Federal Circuit is somehow undermining pharmaceutical research has no basis in fact.

IV. THE FEDERAL CIRCUIT DID NOT VIOLATE RULE 52(a); IT NEITHER IGNORED NOR REWROTE ANY RELEVANT FINDINGS OF FACT

Contrary to Merck's repeated assertions, this is not a case where Rule 52(a) is implicated. Here the Federal Circuit accepted all of the district court findings of fact. The appellate court reversed the district court's decision only because it found that the district court's "conclusion that obviousness had not been proven is incorrect as a matter of law." (App. at 5a.) The Federal Circuit was, therefore, not constrained by the clearly erroneous standard of Rule 52(a). *Bose Corp. v. Consumers Union of United States, Inc.*, 466 U.S. 485, 501 (1984) ("Rule 52(a) does not inhibit an appellate court's power to correct errors of law, including those that may infect a so-called mixed finding of law and fact . . .").

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[3] *See In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985) (obviousness rejection of claims affirmed in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among 'thousands' of compounds"); *In re Susi*, 440 F.2d 442, 445 (C.C.P.A. 1971) (obviousness rejection affirmed where the disclosure of the prior art was "huge, but it undeniably include[d] at least some of the compounds recited in appellant's generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives").

A. The Federal Circuit's Opinion Correctly Characterizes The District Court's Findings About The Disclosure Of The '813 Patent

The centerpiece of the Petition is the unfounded allegation that the Federal Circuit rewrote a key finding of the district court concerning the disclosure of the '813 patent. (Petition at 5-6, 11-12, 15-16.) In support of its position, Merck focuses on a single sentence and ignores the remainder of the fourteen page opinion. The limited focus and the resultant removal of the sentence from the context of other relevant portions of the opinion has totally distorted the meaning of the sentence in question.

The Federal Circuit decision states, in pertinent part, that:

> The district court found that the combination of amiloride and hydrochlorothiazide was disclosed in the '813 patent. 690 F. Supp. at 1383. Further finding that more than 1200 combinations are disclosed and that neither amiloride nor hydrochlorothiazide are highlighted as preferred embodiments of the '813 patent, however, the district court concluded that the combinations claimed in the '430 patent would merely be "obvious to try," and therefore not barred by 35 U.S.C. § 103. We do not quarrel with the factual findings of the district court, but we believe its conclusion that obviousness had not been proven is incorrect as a matter of law.
>
> . . . .
>
> That the '813 patent discloses a multitude of effective combinations does not render any

> particular formulation less obvious. [App. A at 5a-6a.]

The Federal Circuit was thus not stating that the district court had found that the combination of amiloride and hydrochlorothiazide was uniquely disclosed. It was instead stating that the district court found that the combination was one of 1,200 possible described combinations.[4] That is precisely what the district court found when it stated:

> Since the '813 patent discloses in excess of 120 pyrazinoylguanidine [sic] and 10 possible potassium losing diuretics, there are more than 1200 possible combinations, of which the combination of Amiloride and Hydrochlorothiazide would be one. [App. B at 30a.]

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[4] Merck erroneously contends that Biocraft had conceded that the district court had not found that the combination of amiloride and hydrochlorothiazide had been disclosed in the '813 patent. (Petition at 6.) That assertion, however, mischaracterizes Biocraft's position. Before the district court and the Federal Circuit, Biocraft was arguing that because the '813 patent *highlighted* three specific pyrazinoylguanidines, one of which was amiloride, and only one potassium-losing compound, hydrochlorothiazide, that patent described *three* combinations of a pyrazinoylguanidine and a potassium-losing compound, one of the three being amiloride and hydrochlorothiazide, in a unique manner. The district court, in holding that the '813 patent did not indicate a *preference* for either amiloride or hydrochlorothiazide, rejected that contention. The Federal Circuit did not reject the district court finding that there was no preference. It merely held that the lack of such a teaching was irrelevant since, for the purpose of the obviousness analysis, it was not necessary that the amiloride-hydrochlorothiazide combination be described as a preferred composition. (App. A at 6a-7a.)

B. Merck Has Mischaracterized The District Court's Findings Concerning The Properties Achieved By The Claimed Amiloride And Hydrochlorothiazide Combination

Merck grossly mischaracterizes the district court's findings when it alleges that the claimed combination produced an unexpected increase in sodium excretion and that, when "fairly read," the district court's opinion demonstrates that it found that such unexpected results were achieved. (Petition at 12 n.5, see also Petition at 7, 9, 19.) The district court specifically rejected Merck's contention that the patented combination produced an unexpected increase in sodium excretion. (App. A at 9a.) It instead found that the claimed combination only "results in a reduction in the amount of potassium ions that are eliminated, *without a reduction in the amount of sodium ions that are eliminated.*"[5] (App. B at 18a.)

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[5] Merck, relying on *Kelly v. Southern Pacific Co.*, 419 U.S. 318 (1984), asserts that it was error for the Federal Circuit to rely upon the district court's failure to adopt a proposed finding in stating that the trial court had found that the amiloride-hydrochlorothiazide combination did not cause a more than additive increase in sodium excretion. (Petition at 19 n.11.) *Kelly* is, however, inapposite. In that case, the court of appeals apparently based its conclusion that there was no employment relationship between the parties solely on the district court's failure to adopt proposed findings of the petitioner. 419 U.S. at 325, 331-32. In the present case, the Federal Circuit's statement that Merck had not proved a greater than additive effect for sodium excretion was based on the district court's express finding that the combination of amiloride and hydrochlorothiazide produced a decrease in potassium excretion "without a reduction in the amount of sodium ions that are eliminated." (App. A at 9a.) That finding alone would have been sufficient to support the Federal Circuit's statement. However, the appellate court

The district court did find that the '813 patent did not teach "that amiloride and hydrochlorothiazide should be combined to produce the effects as set forth in the '430 patent." (App. B at 29a.) It made similar findings with respect to other prior art. (App. B at 32a.) That is very different from a finding that the patented composition actually achieved those results.

There is, of course, no dispute that the '430 patent *asserts* that the combination of amiloride and hydrochlorothiazide produces unexpected amounts of sodium excretion. However, *the overwhelming evidence established that the claimed combination did not in fact achieve these results* (App. E at 6a-14a, 16a-19a), and the district court so found (App. B at 18a). Consequently, a fair reading of the district court's opinion leads to but one possible conclusion: while that court found that the prior art does not suggest the results asserted in the '430 patent, it also found that the

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also referred to other findings made by the district court and to the lower court's refusal to adopt Merck's proposed finding. (*Id.*) Thus, in this case, unlike *Kelly*, the Federal Circuit's statement was fully supported by specific findings of the district court. That the position was also supported by the district court's refusal to adopt a proposed finding, does not support Merck's position.

Wholly aside from the foregoing, the statement was not even the basis for the Federal Circuit's decision. The statement appears in a portion of the opinion that recounts Merck's ever changing position. It notes that, at trial, Merck had contended that a greater than additive effect was obtained from the patented combination, but that Merck had abandoned that position on appeal. (App. at 9a.) Since Merck was not asserting on appeal that a greater than additive effect was obtained, the Federal Circuit's statement was pure dicta and had no bearing on its decision.

combination of 5 mg. of amiloride and 50 mg. of hydrochlorothiazide did not *in fact* produce unexpected results. The district court thus clearly rejected Merck's contention that the claimed combination actually achieved the unexpected increase in sodium excretion that is alleged in the '430 patent.[6]

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[6] Merck accuses the Federal Circuit of engaging in de novo fact finding when it allegedly stated that, given the teachings of the prior art, the co-administration of amiloride and hydrochlorothiazide was expected to "induce more sodium excretion then would either diuretic alone." (Petition at 17, 19.) Merck fails to advise this Court that the Federal Circuit's comment was made in response to Merck's argument that the evidence demonstrated that the claimed composition caused more sodium excretion than 50 mg. of hydrochlorothiazide alone and that this was an unexpected result. Significantly, as the Federal Circuit noted, this assertion was different than the one advanced by Merck below. (See App. A at 9a.) Thus, the statement in question is simply dicta which points out that, even if Merck's newly created position is correct, it would not impart patentability to the claimed invention.

Merck also characterizes as a de novo finding the Federal Circuit's statement that "the '813 patent instructs the artisan that any of the 1200 disclosed combinations will produce a diuretic formulation with desired sodium and potassium eliminating properties." (Petition at 16.) The assertion is utterly incredible since that fact was never disputed before the district court and that is precisely what the patent teaches when it states:

> It has also been found as another feature of this invention that when co-administered with other diuretic agents known to enhance the elimination of potassium ions along with sodium ions, the novel pyrazinoylguanidines of this invention will reduce the excretion of potassium ions and thus overcome this undesirable property of other diuretic agents. The compounds of this invention, therefore, are useful in

Merck urges two other alleged advantages of the amiloride-hydrochlorothiazide combination. First, it claims that the onsets and duration of action of the two compounds were well-matched, providing certain advantages. (Petition at 9.) Second, it asserts that one of the pyrazinoylguanidine compounds disclosed in the '813 patent (MK-685) was "totally inappropriate" for use in combination with hydrochlorothiazide (Petition at 9 n.3 and 16 n.9.)

There can be little doubt that these alleged "advantages" were induced by the present litigation. The '430 patent does not mention them. Although Merck had completed most of its clinical testing, including the testing of MK-685, the allegedly well-matched characteristics of amiloride and hydrochlorothiazide and the asserted incompatibility of MK-685 and hydrochlorothiazide were not mentioned while the applications that led to the '430 patent were before the PTO. To the contrary, MK-685 is one of the com-

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combination with other classes of diuretic agents to prevent the loss of potassium which the other diuretics would otherwise cause to be eliminated. [Column 3, lines 10-20.]

Moreover, Merck acknowledges that "[t]he '813 patent generally states that the pyrazinoylguanidines will reduce the excess potassium excretion caused by such other [potassium-losing] diuretics." (Petition at 9.) Finally, as noted *infra* at 21, Merck's expert deStevens has unequivocally asserted that the '813 patent suggests that the combination of amiloride and hydrochlorothiazide, the specific combination claimed in the '430 patent, would abate any excessive potassium loss that might otherwise result if hydrochlorothiazide were administered alone. Since hydrochlorothiazide was known to produce adequate sodium excretion, that is an admission that the combination would have desired sodium and potassium eliminating properties.

pounds which the '430 patent specifically states can be substituted for amiloride while still retaining the beneficial results of the patented invention. (Col. 2, ll. 46-55.)

Indeed, Merck did not introduce much evidence at trial concerning these alleged advantages until it became clear, following the testimony of its Medical Director in charge of the clinical studies with the amiloride-hydrochlorothiazide combination, that the alleged unexpected increase in sodium excretion was, in fact, nonexistent at the claimed dosage ranges. (App. E at 6a-14a.) Even then its position constantly shifted. In its first effort to prove that amiloride and hydrochlorothiazide were "well-matched," it urged that the two compounds had the same duration of action. After the evidence demonstrated that hydrochlorothiazide's duration of action was no more than half of amiloride's (App. E at 5a-6a), Merck changed its tune once again. It alleged, as it does now, that amiloride and hydrochlorothiazide were uniquely matched (App. E at 14a-15a).

These "advantages" are thus the type of litigation-induced pronouncements that this and other courts have consistently refused to accept as supporting unobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 25-26 (1966); *In re Vamco Mach. & Tool, Inc.*, 752 F.2d 1564, 1575 (Fed. Cir. 1985); *Schutt Mfg. Co. v. Riddell, Inc.*, 673 F.2d 202, 205 (7th Cir. 1982); *Carter-Wallace, Inc. v. Otte*, 474 F.2d 529, 540-43 (2d Cir. 1972), *cert. denied*, 412 U.S. 929 (1973); *Young Corp. v. Jenkins*, 396 F.2d 893, 895-96 (9th Cir. 1968).

C. The Federal Circuit Did Not Ignore The District Court's Finding Concerning Merck's Expert Witness

Merck correctly notes that the district court found that the testimony of its expert deStevens was "persuasive of the issue of obviousness as it related to the '813 patent." (Petition at 10.) But it wrongly asserts that the Federal Circuit did not accord proper deference to that testimony. (Petition at 19.) The only portion of the testimony that was relevant to the obviousness determination considered by the Federal Circuit supported the district court finding (adopted by the Federal Circuit) that the combination of amiloride and hydrochlorothiazide was one of 1,200 combinations described in the '813 patent. By way of example, in his expert report, deStevens stated:

> The '813 patent suggests that amiloride hydrochloride may be coadministered with hydrochlorothiazide to abate any excessive potassium loss that might otherwise result if hydrochlorothiazide were administered alone. [App. E at 21a.]

Moreover, while deStevens testified that the '430 *patent* taught that the amiloride-hydrochlorothiazide combination produced unexpected results, he never considered whether *the claimed composition* of 5 mg. of amiloride and 50 mg. of hydrochlorothiazide also produced unexpected results. He indicated that a sharp increase in sodium excretion over that which was achieved with hydrochlorothiazide alone would be an unexpected result. He was not prepared to state that only a slight increase in sodium excretion would be unexpected. (App. E at 1a-5a.)

Significantly, as demonstrated in the previous section, the district court rejected Merck's contention

that the claimed amiloride-hydrochlorothiazide combination produced an unexpected increase in sodium excretion. It instead found that the claimed combination "results in a reduction in the amount of potassium ions that are eliminated, without a reduction in the amount of sodium ions that are eliminated." (App. B at 18a.)

The testimony of Dr. deStevens thus *supported* the key findings of the district court which resulted in the Federal Court's reversal, that is that the '813 patent disclosed the amiloride-hydrochlorothiazide combination, albeit as one of 1,200 other possible combinations, and that the claimed composition did not produce an unexpected increase in sodium excretion.

D. The District Court Findings Regarding The Methodology Of Pharmaceutical Research And Lack Of Predictability Of Results In The Diuretic Field Are Also Irrelevant

Merck also alleges that the district court made explicit findings regarding how research was carried out in the pharmaceutical industry and the unpredictability of results in the diuretic field. (Petition at 13-14.) Those findings are, however, irrelevant because they are directed to prior art other than the '813 patent. There is no dispute that the '813 patent expressly teaches that any one of the disclosed pyrazinoylguanidines, one of which is amiloride, can be combined with any one of the disclosed potassium losing compounds, one of which is hydrochlorothiazide, to reduce potassium excretion caused by the potassium-losing compound. As noted in the previous section, Merck's expert deStevens specifically stated that the '813 patent "suggests" that the combination of amiloride and hydrochlorothiazide will "abate any

excessive potassium loss that might otherwise result if hydrochlorothiazide were administered alone." (App. E at 21a.) Indeed, before this Court, Merck acknowledges that the '813 patent generally states that the pyrazinoylguanidines [described in that patent] will reduce the excess potassium excretion caused by [potassium-losing] diuretics." It also concedes, as it must, that amiloride is one of the disclosed pyrazinoylguanidines and hydrochlorothiazide is one of the disclosed potassium losing diuretics. (Petition at 9.) The findings quoted by Merck are thus wholly irrelevant to the obviousness issue resolved by the Federal Circuit.

E. The Federal Circuit Did Not Ignore The District Court Finding That The Patented Product Was A Commercial Success

Merck urges that the district court made findings that the patented composition was a commercial success and notes that this evidence may support the validity of the patent. (Petition at 14.) The Federal Circuit, however, did not ignore that finding. In fact, it acknowledged the finding and noted that such evidence can be an indication of nonobviousness. It held however that, "in the circumstances of this case, where it is the only such indication, it is insufficient to render Merck's claimed invention nonobvious." (App. A at 11a n*.) That ruling is clearly consistent with the precedent of this court. *Sakraida*, 425 U.S. at 282 (the patented invention was obvious even though the invention was "doubtless a matter of great convenience, produced a desired result in a cheaper and faster way and *enjoyed commercial success. . .*" [emphasis added]).

V. THE FEDERAL CIRCUIT DECISION WILL NOT HAVE AN ADVERSE IMPACT ON PHARMACEUTICAL RESEARCH

Merck's allegation that the Federal Circuit decision in this case would somehow have an adverse impact on pharmaceutical research because of an alleged characterization of Merck's research effort as routine experimentation (Petition at 22-24) is plainly without foundation. In the first place, the Federal Circuit did not suggest that Merck's *entire* research effort was merely routine experimentation. As noted above, much of the research effort is wholly irrelevant to the obviousness analysis because it occurred long before the '813 patent disclosure became publicly available. The Federal Circuit's routine experimentation statement applied merely to the methodology used to determine that the commercial and patented composition would contain 5 mg. of amiloride and 50 mg. of hydrochlorothiazide.

In any event, the statement was not a finding of fact; it was merely a response to Merck's assertion that the specific amounts of each ingredient set out in the claims imparted patentability. In response to that argument, the Federal Circuit merely noted that the "evidence at trial showed that, though requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine." (App. A at 10a.) The evidence to which the court referred was the testimony of Merck's own expert, deStevens. (App. A at 11a.) In its petition, Merck pointed to no evidence that the determination of the dosage ranges was anything but routine. Moreover, Merck fails to note that the tests, whether routine or otherwise, merely demonstrated that the claimed

composition achieves precisely the results that the prior art '813 patent teaches would be obtained. Discovering that the prior art teachings are correct is not an unobvious advance which warrants patent protection.

Finally, Merck's research efforts were more than adequately rewarded by the grant of the '813 patent. That patent gave it the right to be free from competition in the sale of an amiloride-hydrochlorothiazide product for seventeen years. The '430 patent extended that period of exclusivity an additional *six* years. Such an extension was clearly not justified by the minimal difference between the subject matter of the '813 and '430 patents.

Congress has decreed that an invention is entitled to only one patent for each patentable invention. 35 U.S.C. §§ 101-103. Research will not be impaired if, as in this case, that statutory decree is followed.

VI. CONCLUSION

For the foregoing reasons, Merck's petition should be denied.

Respectfully submitted,

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October 30, 1989

APPENDIX

[304] Goodfellow - direct

* * *

A. . . . Secondarily, the pharmacokinetics or the duration of action of both components was very nicely matched. So that the duration of hydrochlorothiazide was about 24 hours as was amiloride. There was a very nice fit. And a patient could take MODURETIC—virtually any patient could take MODURETIC once a day. And you can contrast that with dyazide where the duration of hydrochlorothiazide was longer than the duration of Dyrenium, their potassium spearer (sic), or ALDACTAZIDE where the duration of spironolactone to my recollection was much longer than hydrochlorothiazide.

So it didn't fit as well. We really had a true, once a day, antihypertensive product.

* * *

[437] de Stevens - cross

* * *

Q. Do you have the patent—the '430 patent in front of you, sir?

A. Yes. I believe you testified that the results reported in Tables 4 and 5 of the patent were unexpected?

A. Yes.

Q. They were unexpected because of the magnitude of the increase when the combination of amiloride and hydrochlorothiazide was administered on the sixth day of treatment; is that correct?

A. Under the conditions of this experiment.

Q. I'd like to ask you to make an assumption. What if the increase on the sixth day, when the hydrochlorothiazide plus amiloride were administered, was in your view min-

imal, the increase was minimal, would the result have been unexpected?

A. I can't answer the question.

Q. Why not, sir?

A. Because it is an assumption.

Q. You're an expert. I'd like you to make that assumption and answer the question based on the assumption?

A. Not consistent with the facts here. My testimony is based on these facts. My conclusions with regard to the unexpected effect is based on this.

Q. Doctor, I'd like you to assume, though, that the increase

[438] de Stevens - cross

that is obtained in sodium excretion when the combination of hydrochlorothiazide and amiloride are administered on the sixth day was minimal in your view. I'd like you to tell me, based on that assumption, whether you believe the results would have been unexpected?

A. That is a speculation. I don't know—under these same conditions, so on, I don't know what the point—in a speculative question of that type.

Q. I think it is important, sir. I'd like to have your opinion on that.

A. I wouldn't say it is unexpected or expected. I'd just look at it.

Q. You looked at the data in the patent and you said it was unexpected. Isn't that true?

A. Because of the nature of the experiment. We are starting with controls and we are carrying out this experiment over a five-day period giving a certain amount of hydrochlorothiazide per day.

We are—on the fourth and fifth day we are below control values. And then we give amiloride and we get a sharp increase in sodium excretion. That is unexpected.

Q. Well, sir, I'm asking you to assume all the facts you've just stated except one change. We don't have a sharp increase. Instead of the sharp increase we have an increase which is minimal. I would like to now know in your view, in your expert

[439] de Stevens - cross

opinion—you're an expert in this case, sir—whether that would be an unexpected result?

A. No, I don't think it would be unexpected or expected. I wouldn't know what to make of it.

BY THE COURT:

Q. Doctor, let's assume—take a look at Table No. 4, okay?

A. Yes.

Q. Let's assume under the sodium excretion?

A. Yes.

Q. You got it from 257 to 70 on the fifth day?

A. Yes.

Q. The next figure is 177.8. The next one after that is 160.2. Let's assume we get rid of the 100. If it was 77.8 and it was 60.2, would that be an unexpected result or an unexpected effect so far as you were concerned?

A. I would say that the amiloride was inactive.

Q. Would it be expected or unexpected?

A. I don't know until I carry out the experiment, sir. You see, I have to carry out the experiment. I get the result.

Q. This is the experiment. It is there?

A. Yes. I get 77—

Q. Instead of 177—you said it was unexpected that you got 177, correct?

A. Yes.

Q. Now I'm saying: Assuming it is 77, is that as equally

[440] de Stevens - cross

unexpected?

A. No.

Q. That would be expected?

A. No. It would show me that the compound may be inactive when mixed with hydrochlorothiazide.

THE COURT: Go ahead. Mr. Bajefsky.

(Pause.)

THE COURT: What if it went below 70 to 60?

THE WITNESS: I think I'd start to look at this very closely, this combination. Something is going wrong. In other words, it is totally inactive. It is doing nothing.

THE COURT: That would be unexpected?

THE WITNESS: I don't know until I carried out the experiment.

THE COURT: I'm saying: That is the experiment. You carried out the experiment. That is the length and breath of your experiment. Your experiment shows the figure to be 77 instead of 177.

You had no problem saying that when the number was 177 that was unexpected. Why was it unexpected?

THE WITNESS: Because what you had done over a period of five days was to give this dose of hydrochlorothiazide, 100 milligrams each day and you're depleting it

down below controls. And then when you give the amiloride you get a sharp increase.

[948] Mrozcek - direct

* * *

Q. Doctor, I'd like to return now to Exhibit 275. Again to the pages for MODURETIC. In particular, I would like you to read the two sentences beginning on the tenth line of the amiloride clinical pharmacology section.

A. We're on which page? 1322. 1322. Which line, sir?

Q. It's the tenth line of the amiloride clinical pharmacology section. It begins, "Amiloride"—

A. "Amiloride HCl usually begins to act within two hours after an oral dose. It's effect on electrolyte excretion reaches a peak between six and ten hours and lasts about 24 hours."

Q. I'd also like you to read the two sentences that begin on the seventh line of the hydrochlorothiazide clinical pharmacology section.

A. "The onset of diuretic action of hydrochlorothiazide occurs in two hours and a peak action in about four hours. Diuretic activity lasts about 6 to 12 hours. Hydrochlorothiazide is eliminated rapidly by the kidney."

Q. There has been testimony in this case that amiloride and

[949] Mrozcek - direct

hydrochlorothiazide have the same duration of action. Is that testimony correct?

A. Well, not according to the Physicians' Desk Reference information here.

Q. What does that tell you about the duration of action of these two drugs?

A. That hydrochlorothiazide lasts maximum 12 hours and the amiloride acts for 24 hours.

Q. Is there any advantage in amiloride having a duration of action from 12 to 18 hours longer than hydrochlorothiazide?

A. Not that I can imagine. The main use of amiloride should be to block the potassium excretion while the hydrochlorothiazide is working.

Q. Why is the main advantage of the amiloride while the hydrochlorothiazide is working?

A. Well, if one is looking to block potassium excretion, one wants to put potassium—the blockage of potassium excretion to occur while sodium is going through the tubule, as Dr. Preuss had pointed out. Actually, after the diuresis by the hydrochlorothiazide is over, there really isn't going to be any sodium in the distal tubule at the sodium-potassium exchange sites to be the amiloride or the potassium blocking agent to have any effect upon it.

[1018] Wilkinson - direct

* * *

Q. Now, isn't it further true that almost three years later than this document you concluded, you, yourself, concluded, not that the clinical studies established synergism, but that the studies demonstrated that the combination of amiloride and hydrochlorothiazide had the same overall pattern of safety and effectiveness as hydrochlorothiazide and that the only essential difference in action was on the serum potassium levels?

A. I have to see the context in which I made this conclusion.

Q. I'll show it to you. I'd like you to look at DTX-204.

A. Just a minute.

Q. Is this a document that you generated, Dr. Wilkinson?

A. It would appear to be so.

Q. And the date is July 29, 1969?

A. Yes.

Q. And it deals with the status of future studies for amiloride?

A. Yes.

Q. Okay. Now, I'm going to be reading something to you. I just want to know. CO-HydroDIURIL is the name that Merck had given at the time for amiloride in combination with hydrochlorothiazide?

A. Correct.

Q. And HydroDIURIL is hydrochlorothiazide alone. Correct?

A. Correct.

Q. Now, the last paragraph on the first page. I will read it. I'll read the first sentence of that paragraph.

It says, "In general, these studies demonstrate that CO-HydroDIURIL has the same overall pattern of safety and effectiveness as HydroDIURIL and that the only essential differences in action are upon serum potassium levels."

Did I read it correctly?

A. Correct.

* * *

[1020] Wilkinson - direct

* * *

Q. Is that a correct characterization of what you wrote at that time and what you believed at that time?

A. Apparently so.

Q. All right.

Now, when you are talking of these studies, am I further correct that the antecedent for that word are the studies earlier referred to in the first four paragraphs of that letter?

A. Yes.

Q. All right.

Q. So as of this date, what you were basically saying was, as I understand it, that the studies you had concluded demonstrated both from a safety and effectiveness standpoint that the only essential differences between the combination of amiloride and hydrochlorothiazide, as compared with hydrochlorothiazide alone,

[1021] Wilkinson - direct

was upon serum potassium levels; correct?

A. I have had a chance to read the memo.

Q. Please.

A. I think you have to put the last paragraph into, first, the context of—the purpose of its writing.

Q. Fine.

A. Dr. Robinson had assumed responsibility for the medical group, Dr. Lawrason having been given other responsibilities.

This page is attempting to encapsulate a tremendous amount of work that had already occurred. There were

two general phases of these studies. The earlier phases had been studies conducted by very well-known clinical investigators primarily using their own protocols and these studies tending to be in more seriously ill patients.

We had encountered a worrisome number of adverse findings. In particular, hyperkalemia would worry one with a drug of this nature. This could be a very dangerous adverse effect to a drug of this type.

Later studies, this second phase, which I referred to in the fourth paragraph down, the second generation of studies, we were purposely seeking less seriously ill patients in the so-called phase III type studies. And these were in—the results generally were comparable to the effects one might see with the thiazides. The adverse reaction frequency.

The doses that we had selected also were such that the

[1022] Wilkinson - direct

addition of these two drugs, the co-administration of these two drugs, gave effects both in terms of safety and efficacy that were not remarkably different from those that one would have seen with hydrochlorothiazide given alone.

Q. And that conclusion—correct me if I'm wrong—was reached on the basis of all of this data?

A. It was a summation by me for the man assuming responsibility for all the clinical studies of all the drugs and trying to get it down to one page.

Q. Isn't it true that this same characteristic in this last paragraph is applicable to the MODURETIC drug that is on the market today?

A. In general, I would believe it's very close to what we see with MODURETIC today. Yes.

* * *

[1027] Wilkinson - direct

* * *

Q. Fine. I would like you to look again at the exhibit we were talking about. I believe, at the end of the day, Defendant's Exhibit 204, which is in Volume 2. Do you have that exhibit?

A. Yes.

Q. We were looking at the last paragraph on the first page of that exhibit. Just so that we can get back to where we were, I will read again the first sentence of that paragraph. I will alert you to the fact that yesterday we read two sentences at the request of the Judge.

I want to ask you a question, one more question about the first sentence. I'll read it: "In general, these studies demonstrate that CO-HydroDIURIL has the same overall pattern of safety and effectiveness as HydroDIURIL and that the only essential differences in action are upon serum potassium levels."

Do you see that?

A. Yes.

Q. All I want to know now, to supplement what we covered yesterday in court, is that that includes—when you are talking about the same overall pattern of safety and effectiveness as HydroDIURIL, that includes sodium excretion, does it not?

A. It certainly is implicit in the statement.

Q. That is what you intended?

[1028] Wilkinson - direct

* * *

A. Yes.

* * *

[1036] Wilkinson - direct

* * *

Q. Now, on page 105689, which is the second page, paragraph 2—do you see that at the top of the page?

A. Yes.

Q. Now, just so the record will be clear. MK-870 is amiloride. Correct?

A. Correct.

Q. This paragraph, as I read it, says, "The diuretic effects of MK-870 are additive to those of hydrochlorothiazide and ethacrynic acid. And because of the antikaliuretic activity, this potentiation of diuresis can be accomplished without increased potassium secretion."

Did I read that correctly?

A. Yes.

Q. In fact, Dr. Wilkerson (sic), isn't it true that you ultimately concluded that your amiloride-hydrochlorothiazide combination was not effective even to provide significant additive natriuretic and diuretic results at practicably usable doses of amiloride?

* * *

[1037] Wilkinson - direct

* * *

A. Yes. But the doses that we utilized in the great bulk of studies were primarily to provide an additional information on the safe use of the drug.

I think we also knew—my recollection is that we always knew we could get significant enhancement of sodium excretion. But from a practical point of view, it would be at the expense of safety.

So that we kept the doses low, restricted. So the statement as it stands is I think an accurate one, that the drug behaved in terms of safety and effectiveness very similar to that of hydrochlorothiazide except that it did retain the potassium wastage that would have been associated with hydrochlorothiazide by itself.

So the answer is basically yes.

Q. Okay. Now, let me just refer you to DTX-191. That is in the first volume.

A. Right. I have it.

Q. Am I correct, Dr. Wilkerson (sic), that that is a document that you in the normal course of business would have generated on or about the date indicated?

A. I would assume so. Yes.

Q. And the date indicated, as I read it is, is July 19, 1968.

A. Correct?

Q. Now I'd like to read into the record the second paragraph of

[1038] Wilkinson - direct

that letter, but I would note if you feel you would like to read the entire letter, please feel free to so so. But the second paragraph reads as follows:

"Studies set up in 1965 and 1966 formed the basis for the New Drug Application with claims limited to three areas; hypertension, congestive heart failure, and cirrhosis with ascites," a-s-c-i-t-e-s. "Doses most commonly employed were 10 or 20 milligrams per day on a b.i.d. schedule. The objectives mandated by marketing requirements were effective antikaliuretic action when the drug was used with thiazides or more potent saluretic-diuretic agents and a sparing of dosage requirements of these agents. The first objective was achieved, but the second was not; hyper-

kalemia occurred at a prohibitively high rate at doses that were adequate to produce adequate additive and diuretic activity."

Did I read that correctly?

You're here talking about the combination of amiloride and other—and a thiazide?

A. And ethacrynic acid. Both combinations.

Q. That was actually hydrochlorothiazide, right?

A. Correct.

Q. Is this last sentence, here, this last statement.

"Hyperkalemia occurred at a prohibitively high rate at doses that were adequate to produce adequate additive, natriuretic and diuretic activity."

[1039] Wilkinson - direct

Was that statement the basis for your agreement with my question just a few minutes ago, that you finally concluded that your amiloride-hydrochlorothiazide combination was not effective even to provide significant additive natriuretic and diuretic results at practicably usable doses of amiloride?

A. Yes.

Q. And isn't it true that what would happen, if you used doses high enough to give you adequate additive natriuretic and diuretic activity, you would generate hyperkalemia in patients? Is that right?

A. You have to get back to the kind of patient you're talking about, too. It isn't a simple matter. But essentially you are correct.

Q. What would happen if they get hyperkalemia? They might die?

A. Yes.

Q. Therefore, it wasn't practicably usable at that rate?

A. The doses that are being discussed here are implicitly whether one would combine 5 or 10 milligrams of amiloride with 50 milligrams of hydrochlorothiazide. It's not stated, but as one sees, 10 or 20 on a twice daily schedule. 50 milligrams twice a day was the customary dose of hydrochlorothiazide.

So you're talking basically about a 5-50 or a 10-50 combination. And it was my strong feeling at the time that the 5-50 was a much more practical dose for wide use of the drug.

Q. Because while that wouldn't give you significantly additive

[1040] Wilkinson - direct

effects, it wouldn't create the hyperkalemia problem?

A. Correct.

* * *

[1335] Cragoe - direct

* * *

Q. Dr. Cragoe, would you turn to the next exhibit in your book, DTX-275?

A. Yes. I have.

Q. Dr. Cragoe, do you have Exhibit 275 before you?

A. Yes.

Q. In particular, would you look at page 1322? The page numbers are in the upper left-hand corner.

A. Yes. I have it.

Q. Can you tell me how soon after oral administration amiloride begins to work?

A. It says here amiloride-hydrochlorothiazide usually begins to act within two hours after an oral dose.

Q. When does amiloride reach its peak effect on electrolyte excretion?

A. The next sentence says: Its effect on electrolyte excretion reaches a peak between 6 and 10 hours.

Q. What is amiloride's duration of action?

A. The same sentence indicates it lasts about 24 hours.

Q. Now, Dr. Cragoe, when does hydrochlorothiazide begin to work following oral administration?

A. This indicates that the onset of diuretic action of

[1336] Cragoe - direct

hydrochlorothiazide occurs in two hours. And its peak action is in about four hours and that it lasts from 6 to 12 hours in its action.

Q. What do the onsets of activity times the peak action and durations of action of amiloride and hydrochlorothiazide mean as far as their suitability as diuretic drugs to be put together into a single composition?

* * *

A. Well, we felt this was virtually an ideal combination. The two drugs both begin their action at about the same time; that is, about two hours. They move along towards their peak at about the same rate. The action of amiloride continues a little after that after the hydrochlorothiazide is already over. Therefore, it is continually going to act against the potassium loss. And the entire effects are over within 24 hours permitting a one day—once a day use of the drugs.

DEFENDANT'S
EXHIBIT DTX-191

MEMO

TO	J.A. Page, M.D.	Location West Point
FROM	W.H. Wilkinson, M.D.	Location West Point
SUBJECT	Present Objective of MK-870 Clinical Studies	Date 7/19/68

You will recall that we recently briefly reviewed the present status of studies with Colectril and the two combinations presently under investigation. I felt that it might be useful for you to receive a distillation of our present plans for the clinical trial of this compound.

Studies set up in 1965 and 1966 formed the basis for the New Drug Application, with claims limited to three areas; hypertension, congestive heart failure, and cirrhosis with ascites. Doses most commonly employed were 10 or 20 mg./day, on a b.i.d. schedule. The objectives mandated by marketing requirements were effective antikaliuretic action when the drug was used with thiazides or more potent saluretic-diuretic agents and a sparing of dosage requirements of these agents. The first objective was achieved, but the second was not; hyperkalemia occurred at a prohibitively high rate at doses that were adequate to produce adequate additive natriuretic and diuretic activity.

* * *

M129335

DEFENDANT'S
EXHIBIT DTX-204

MEMO

TO:	Dr. H.J. Robinson	W 42-3
FROM:	Dr. W.H. Wilkinson	W 42-3
SUBJECT:	MK-870-Status of Future Studies	Date: 7/29/69

We are approaching completion of individual summaries of studies performed with Colectril® ,CO-HydroDIURIL® and CO-Edecrin® . Your remarks yesterday indicate that decisions as to the future of this family of drugs are to be considered by MSD in the immediate future.

* * *

In general, these studies demonstrate that CO-Hydro-DIURIL® has the same overall pattern of safety and effectiveness as HydroDIURIL® and that the only essential differences in action are upon serum potassium levels. At minimal added risk the potassium depletion that occurs with thiazide administration is averted.

M162548

DEFENDANT'S
EXHIBIT DTX-233

* * *

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-200
18-201

Jul 29 1981

Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
Attention: Charles P. Balant, Ph.D.
West Point, Pennsylvania 19486

Dear Dr. Balant:

Please refer to your new drug applications dated February 9, 1979 (18-200) and March 30, 1979 (18-201) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Midamor (amiloride hydrochloride, 5 mg) Tablets and Moduretic (amiloride hydrochloride, 5 mg and hydrochlorothiazide, 50 mg) Tablets.

* * *

M355207

* * *

Labeling should indicate clearly the risk of hyperkalemia and means of minimizing it, the limited dosage range that has been shown useful, the limited added diuretic or antihypertensive effect when amiloride is added to thiazides, and the limited basis for recommending prophylactic use of amiloride, and the lack of evidence that amiloride is a safe agent used alone, at least in most cases. We have attached labeling for amiloride revised to include this information, and also ask you to incorporate the following sections:

Indications

* * *

Amiloride has minimal diuretic or antihypertensive effects when added to a thiazide diuretic and is a weak diuretic/antihypertensive when used alone.

* * *

M355208

* * *

Sincerely yours,

/s/ M.J. Finkel

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs

M355210

PLAINTIFF'S
EXHIBIT PTX-385

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

HON. DICKINSON R. DEBEVOISE

Civil Action No. 85-5585 (DRD)

MERCK & CO., INC.,

Plaintiff,

v.

BIOCRAFT LABORATORIES, INC.,

Defendant.

EXPERT REPORT
OF
GEORGE DESTEVENS

* * *

The '813 Patent

The '813 patent describes certain (3-amino-5,6-disubstituted-pyrazinoyl) guanidines as diuretic agents. Amiloride hydrochloride is specifically disclosed at Examples 89 (col. 31 and footnote, col. 38) and 207 (col. 49, 11. 25-40), and is the subject of claim 11 (col. 51, 1. 44). The specification states that the compounds of the invention when given alone "selectively enhance the excretion of sodium ions without causing an increase in excretion of potassium ions." (col. 2, 1. 65 to col. 3, 1. 2). It is further stated that "[i]t is also contemplated to combine compounds of this invention in unit dosage form with other known diuretic agents, such as, hydrochlorothiazide, ..." (col. 49,

11. 44-46). Example 208 (col. 49, 11. 52-67) describes the formulation of a capsule containing 50 mg of hydrochlorothiazide and 50 mg of (3-amino-5-isopropylamino-6-chloropyrazinoyl)-3,3-dimethylguanidine hydrochloride. The specification also teaches that, in combination with certain other classes of diuretic agents, the pyrazinoylguanidines will

- 16 -

reduce the loss of potassium ions caused by the other diuretics (col. 3, 11. 9-19).

This reference suggests that amiloride hydrochloride may be coadministered with hydrochlorothiazide to reduce the potassium loss that might otherwise be induced if hydrochlorothiazide were administered alone. The '813 patent does not, however, suggest that this combination would cause the unexpected results for sodium excretion and the ratio of sodium to potassium excretion that are achieved by the invention of the '430 patent. The results so described, therefore, would not have been obvious to one of ordinary skill in the art based on the teachings of the '813 patent.

* * *

- 17 -

* * *

August 14, 1987 /s/ George deStevens
Date George deStevens

- 30 -

Supreme Court, U.S.
FILED
NOV 6 1989
JOSEPH F. SPANIOL, JR.
CLERK

No. 89-368

IN THE
Supreme Court of the United States
OCTOBER TERM, 1989

MERCK & CO., INC.,
Petitioner,

v.

BIOCRAFT LABORATORIES, INC.,
Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITIONER'S REPLY BRIEF

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November 6, 1989

* Counsel of Record

WILSON - EPES PRINTING CO., INC. - 789-0096 - WASHINGTON, D.C. 20001

STATEMENT PURSUANT TO RULE 28.1

The subsidiaries (except wholly-owned subsidiaries) and affiliates of Petitioner Merck & Co., Inc. are as previously identified on page ii of the Petition For A Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit filed on September 5, 1989 in this case.

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Rule:

Fed. R. Civ. P. 52(a) 1, 2, 3, 4, 7

IN THE

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No. 89-368

MERCK & CO., INC.,

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On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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PETITIONER'S REPLY BRIEF

PRELIMINARY STATEMENT

Petitioner Merck & Co., Inc. ("Merck") respectfully submits this Reply Brief (i) in further support of its belief that this Court should issue a Writ of Certiorari to review the Federal Circuit majority's conduct in this case, and (ii) to address several arguments first raised in the Opposition Brief filed by Respondent Biocraft Laboratories, Inc. ("Biocraft"). Merck maintains that there is an urgent need for this Court to exercise its supervisory authority over the Federal Circuit and address on the merits that Court's improper entry of *de novo* fact findings and reversal of trial court findings without proper regard to Rule 52(a) of the Federal Rules of Civil Procedure. And, the Federal Circuit majority's decision here

looms as dangerous precedent that threatens to serve as a disincentive which will discourage the pharmaceutical industry from engaging in the painstaking and costly research essential to the discovery of the medicines critical to human health.

It is respectfully submitted that Biocraft's arguments do not undercut the importance of this case or the need for this Court to consider the two questions presented by Merck's Petition.

ARGUMENT

I. THE FEDERAL CIRCUIT MAJORITY ENGAGED IN IMPROPER DE NOVO FACT FINDING AND IGNORED RULE 52(a)

In an effort to sustain a Federal Circuit majority opinion that does not even attempt to demonstrate that a single finding of fact entered by the District Court was "clearly erroneous"—indeed, the majority does not even mention Rule 52(a) of the Federal Rules of Civil Procedure—Biocraft asserts that "the clearly erroneous standard of Rule 52(a) is not an issue." (Bio. Opp. Br. at 2).[1] Like the majority, Biocraft attempts to side-step both Rule 52(a) and the critical and time-honored distinction between the proper functioning of federal trial and appellate courts. And, Biocraft—as it must in its effort to sustain the Federal Circuit majority's invasion of the exclusive fact finding province of the District Court—ignores the irreconcilable differences between the facts as found by the District Court and the majority's *de novo* findings upon which it grounded its reversal. (Pet. at 10-17).[2]

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[1] Biocraft's October 30, 1989 Brief in Opposition to Petition for Writ of Certiorari will be cited as "Bio. Opp. Br. at ——."

[2] Merck's September 5, 1989 Petition for a Writ of Certiorari will be cited as "Pet. at ——."

The critical factual findings of the District Court—and the dichotomous facts employed by the majority to reach an opposite conclusion—were set forth in some detail in the Petition, and Merck will not needlessly repeat those differences here. In sum, the District Court found that:

(i) the prior art '813 patent did *not* disclose the patented combination of amiloride and hydrochlorothiazide (App. B at 25a n.1);

(ii) the art was unpredictable and did not forecast the results produced by the '430 invention (App. B at 28a-29a, 33a); and

(iii) the prior art '813 patent contained no "hint" as to the proportions of amiloride and hydrochlorothiazide recited in Claim 3 of the '430 patent and contained in Merck's commercially successful product, Moduretic®—i.e., 5 mg of amiloride and 50 mg of hydrochlorothiazide (App. B at 30a).

The Federal Circuit majority did not determine any of those findings to be "clearly erroneous"—which it was required to do, pursuant to Rule 52(a), if it wished to set aside those findings. Indeed, the majority announced that it did "not quarrel with the factual findings of the district court." (App. A at 5a). Yet, it cannot be denied that, in truth, the majority expressly or impliedly set aside each of those crucial District Court fact findings and improperly made *de novo* findings of fact.

For example, the District Court findings above are irreconcilable with the Federal Circuit majority's factual assertions that:

(i) the amiloride/hydrochlorothiazide combination was not novel because it was disclosed in the prior art '813 patent (App. A at 5a);

(ii) the results achieved by the amiloride/hydrochlorothiazide combination were expected based upon the prior art '813 patent (App. A at 9a); and

(iii) the experimentation needed to arrive at the claimed dosages of 5 mg of amiloride and 50 mg of hydrochlorothiazide was nothing more than "routine" (App. A at 10a).

Clearly, under the guise of reviewing and reversing the District Court's conclusion of non-obviousness "as a matter of law" (App. A at 5a), in reality the Federal Circuit ignored Rule 52(a) and its proper, limited role as an appellate court.

II. THE FEDERAL CIRCUIT MAJORITY'S DE NOVO FINDINGS WERE ESSENTIAL TO ITS REVERSAL

Apparently recognizing the tenuous nature of its contention that "this is not a case where Rule 52(a) is implicated" (Bio. Opp. Br. at 13), Biocraft devotes a substantial portion of its opposition to an effort to convince this Court that the majority's conduct in entering *de novo* factual findings in this case need not be reviewed because those improper findings were not essential to the majority's reversal. Biocraft attempts to distract attention from the critical importance of the Federal Circuit's new findings by claiming that they were mere dicta. (*See* Bio. Opp. Br. at 17 n.5 and at 18 n.6). Nothing could be further from the truth.

Each of the *de novo* findings set forth in Point I, *supra*, was essential to the majority's rationale. Indeed, the concluding sentence of the majority's opinion on the merits unquestionably establishes that those findings were critical to the majority's decision:

> "Reached by means of *routine procedures*, and producing only *predictable results*, the *recited dosages* therefore do not distinguish the claims of the '430 patent from the amiloride/hydrochlorothiazide combination that the district court properly found was *disclosed* in the '813 patent." (App. A at 11a). (Emphasis added, citation omitted).

Without the improper *de novo* factual findings it entered on appeal, the majority could not have reached the conclusion to reverse. Thus, Merck respectfully submits that this case warrants the attention of this Court not only because an incorrect result has been reached, but because that result was reached only after the Federal Circuit—as it has in the past—overstepped the bounds of proper appellate review and invaded the District Court's province as the finder of fact.

III. THE FEDERAL CIRCUIT MAJORITY, AND BIOCRAFT IN OPPOSITION, IGNORED THE PRESUMPTION OF VALIDITY AND REVERSED THE BURDEN OF PROOF

Merck's '430 patent, like any other patent duly issued by the United States Patent and Trademark Office, was entitled to the statutory presumption of validity as set forth in 35 U.S.C. § 282:

> "A patent shall be presumed valid. . . . The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity."

And, it is axiomatic that this statutory presumption of validity can be overcome only where the party challenging the patent (here, Biocraft) offers "clear and convincing" evidence of the facts necessary to a conclusion of invalidity. *Jones v. Hardy*, 727 F.2d 1524, 1528 (Fed. Cir. 1984).

Yet, here both the Federal Circuit majority, as well as Biocraft in its arguments before this Court, improperly have shifted the burden to Merck to prove that the '430 patent claimed invention was patentable. Thus, Biocraft argues its one-sided presentation of the evidence at length in an effort to sustain the majority's *de novo* findings and faulty analysis. (*See, e.g.*, Bio. Opp. Br. at 16-24). For

example, Biocraft argues at length that "*the overwhelming evidence established that the claimed combination did not in fact achieve these results* [i.e., unexpected amounts of sodium excretion]." (Bio. Opp. Br. at 17). (Emphasis in original). But, what Biocraft—and the Federal Circuit majority before it—ignores is that Merck was under no obligation to prove unexpected results at trial. Rather, the burden was on Biocraft to prove to the District Court—by clear and convincing evidence—that no unexpected results were achieved. Biocraft failed to convince the District Court, and the District Court made no finding that the '430 patented combination did not achieve unexpected results. Indeed, while the District Court did not enter an express finding that unexpected results were achieved by the specific combination employed in Merck's Moduretic®, fairly read the District Court's opinion reveals that it indeed found that the amiloride/hydrochlorothiazide combination caused increased sodium excretion which could not have been forecast based upon the prior art.[3]

Biocraft's Opposition is replete with arguments as to what was established by the trial evidence. In essence, Biocraft argues that the evidence supported the majority's view of the facts. Obviously, Merck—and the District Court—are of a different opinion as to what was proven by the trial evidence. But, that is not the issue. An appellate court is not free to substitute its view of the evidence for that of the District Court. *Anderson v. City of Bessemer City, N.C.*, 470 U.S. 564, 573 (1985). And, even where the trial evidence could be construed to

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[3] Biocraft cannot point to a single District Court finding to support the naked assertion that the District Court "found" that the patented combination did not cause more sodium excretion than would have been expected. (Bio. Opp. Br. at 4). To the contrary, the evidence introduced at trial did lead the District Court to enter the factual findings set forth in detail in Merck's Petition at 11 n.5.

support either party's factual assertions, the District Court's choice between the conflicting views of the evidence must be sustained because it cannot be regarded as clearly erroneous. *Id.*, 470 U.S. at 573-75.

Moreover, arguments as to what the trial evidence established are inappropriate at this stage of the proceedings. The question is whether the majority was entitled to ignore Rule 52(a) and contravene the precedents of this Court by disregarding key factual findings of the District Court and making *de novo* findings. Merck will refrain from arguing the evidence, hoping to have the opportunity to make those arguments in its brief on the merits.

IV. THE MAJORITY INVALIDATED MERCK'S VALUABLE '430 PATENT EVEN THOUGH THE INVENTION WAS MERELY OBVIOUS TO TRY, ESTABLISHING A PRECEDENT WHICH WILL UNDERCUT THE INCENTIVES FOR PAINSTAKING PHARMACEUTICAL RESEARCH

In its Petition, Merck articulated how the Federal Circuit majority's opinion is a dangerous precedent, undermining the validity of patents directed to pharmaceutical compositions and potentially discouraging the costly research required to discover new and beneficial medicines. (Pet. at 22-27). In particular, the majority held obvious Merck's commercially successful diuretic composition, Moduretic®, even though that composition was but one of over 1200 combinations that were merely "obvious to try." Biocraft's arguments in opposition do not detract from the serious disincentives created by the majority's opinion.

Biocraft argues that the Federal Circuit overall has had a positive impact on the value of patents by creating a climate more favorable to sustaining their validity. (Bio. Opp. Br. at 11-12). That, however, is entirely beside the point. The Federal Circuit's function is not and

should not be either pro- or anti-patent; it should be to decide cases correctly through the proper exercise of its role as an appellate court. *See Graver Mfg. Co. v. Linde Co.*, 336 U.S. 271, 279 (1949), *aff'd on rehearing*, 339 U.S. 605, *reh'g denied*, 340 U.S. 845 (1950) (same deference is due to trial court findings which overturn claims as to findings which sustain them).

Biocraft also argues that the Federal Circuit has upheld patents "in the pharmaceutically related areas", citing two Federal Circuit decisions. (Bio. Opp. Br. at 12). Not only is that argument meritless, but the cases relied upon by Biocraft do not even deal with the unique and specialized field of pharmaceutical chemical compositions for human consumption.[4]

Because of the potential industry-wide significance of this case, this Court should grant Certiorari.

---

[4] Biocraft also repeatedly urges that Merck received two patents (the prior art '813 patent and the '430 patent-in-suit) for the same invention. (Bio. Opp. Br. at 3, 12-13, 25). That argument is incorrect and irrelevant here, having formed no part of the Federal Circuit majority's opinion.

CONCLUSION

Merck respectfully submits that each question presented in its Petition has significance that reaches beyond both Merck and Biocraft and deserves this Court's consideration. The proper role of the Federal Circuit in reviewing district court fact findings which underlie the obviousness issue has never been addressed on the merits by this Court and requires clarification. Moreover, the potential negative impact of the majority's decision on the pharmaceutical industry is a significant question of far-reaching concern.

Accordingly, it is respectfully urged that Merck's Petition should be granted and a Writ of Certiorari should issue.

Respectfully submitted,

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